THE SURGICAL CLINICS OF NORTH AMERICA

AUGUST 1975

REGENT DEVELOPMENTS IN ANESTHESIA

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THE SURGICAL CLINICS OF NORTH AMERICA

VOLUME 55 / NUMBER 4
AUGUST 1975

SYMPOSIUM ON
RECENT DEVELOPMENTS IN ANESTHESIA

Harry Wollman, M.D., and
D. Eric Greenhow, M.D., *Guest Editors*

W. B. SAUNDERS COMPANY — Philadelphia · London · Toronto

W. B. SAUNDERS COMPANY: West Washington Square
Philadelphia, Pennsylvania 19105

12 Dyott Street
London, WC1A 1DB

833 Oxford Street
Toronto, Ontario M8Z 5T9, Canada

Library of Congress Cataloging in Publication Data
Main entry under title:

Symposium on recent developments in anesthesia.

(The Surgical Clinics of North America; v. 55, no. 4)
Includes index.
1. Anesthesia. 2. Anesthetics—Physiological effect. I. Wollman, Harry. II. Greenhow, D. Eric. III. Series. [DNLM: 1. Anesthesia. W1 SU764L v. 55 no. 4 / WO200 S9893]
RD34.S85 vol. 55, no. 4 [RD81] 617'.008s [617'.96]
75-14161

The Surgical Clinics are also published in translated editions by the following:

Spanish	Nueva Editorial Interamericana, S.A. de C.V., Cedro 512, Apartado 26370, Mexico 4, D.F., Mexico
Italian	Piccin Editore, Via Porciglia 10, 35100 Padua, Italy
Turkish	Guven Bookstore, Mudafaa Cad. 16-B, P.O. Box 145, Kizilay, Ankara, Turkey

THE SURGICAL CLINICS OF NORTH AMERICA
August 1975 Volume 55—Number 4

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The following information is published in accordance with the requirements of the United States Postal Code.

The Surgical Clinics of North America is published every other month by W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105, at Hampton Road, Cherry Hill, New Jersey 08034. Subscription price is $27.00 per year. Second-class postage paid at Cherry Hill, New Jersey 08034.

This issue is Volume 55, Number 4.

The editor of this publication is Paul D. Dolgert, W. B. Saunders Company, West Washington Square, Philadelphia, Pennsylvania 19105.

Library of Congress catalog card number 39-19714.

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Foreword

In the 10 years since anesthesia was last discussed in the *Surgical Clinics,* major developments have taken place. Some of these developments were to be expected. New anesthetic agents and techniques have emerged, and as more of these have proven to be satisfactory, the continuing use of any of the explosive agents has been questioned more critically. Each of these new and relatively satisfactory agents has its own potential complications and the field of anesthetic toxicity has emerged as a major area of concern to anesthesiologists and surgeons.

The new understanding of drug effects on organs and tissues which is inevitable with the passage of time has occurred. Specific techniques have been improved and new agents developed. Formerly inoperable patients can now be safely anesthetized. Along with this new understanding and these new capabilities has come the movement toward subspecialization within anesthesia. Individuals in large university centers now may practice only pediatric anesthesia or obstetrical anesthesia or, in other cases, cardiac or neurosurgical anesthesia. As might be expected in each of these subspecialties, new and clinically relevant knowledge has come to light rapidly. Anesthesiologists have in addition become deeply involved in totally new areas—the Intensive Care Unit, monitoring, and chronic pain therapy.

Other developments just as important have been perhaps less inevitable. These unexpected developments have included the burgeoning field of biotransformation. The metabolism of general anesthetic agents, which was formerly assumed not to take place at all, has turned out to be an important factor. In fact, metabolic fragments may in some cases be responsible for toxic reactions. Ecologic issues such as operating room air pollution and operating room physical hazards have become topics of concern to the entire operating team. Trace concentrations of anesthetics in the operating room may be related to the incidence of abortion, teratogenesis, or instances of mental effects in operating room personnel.

The present issue of *Surgical Clinics* is not a textbook of anesthesia for there is much that could not be included. Intensive care and monitor-

ing are hardly touched upon; pediatric and obstetrical anesthesia have been omitted completely. What has been covered are three major areas. The first section concerns new knowledge of the effects of anesthetic drugs on organs and tissue. The second section covers some of the newer anesthetic drugs and techniques and includes within it some of the new information which has arisen from the anesthetic subspecialties. The final section concerning special topics in anesthesia deals with some of the areas which we understand least well – the ecologic issues, the post-anesthetic complications which we are only now learning to treat effectively, the management of chronic pain problems, and the question of whether or not explosive agents are needed at all in the practice of anesthesia. We believe this volume provides an overview of what is new and changing in anesthetic practice in 1975. We see it to be very different from the relevant issues in anesthesia in 1965, and we would hope, if the field of anesthesia remains healthy, that this volume will be completely outdated 10 years from now.

D. Eric Greenhow, M.D., and
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Guest Editors

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Effect of Anesthetics on the Heart

*Robert G. Merin, M.D.**

Any drug which depresses central nervous system function sufficiently to be called an anesthetic can also depress the function of the heart. However, there are quantitative differences in these effects. In addition, the intact animal (including man) responds to the administration of different anesthetics with different reflex effects. Consequently, the overall effects of anesthetic drugs on cardiac function can be quite different.[31]

This review will concentrate on what is known about the effects of anesthetics on cardiac function in man, referring only where necessary to animal studies.

HEART RATE AND RHYTHM

Although the rate of cardiac contraction is depressed in a dose-related manner by anesthetics in isolated hearts or heart-lung preparations,[12] the effect in intact animals and man is less predictable. This results from the fact that heart rate in the intact animal is determined largely by the relationship between sympathetic and parasympathetic nervous effects on the heart. Man's slow heart rate at rest (60 to 80 per minute) is a result of tonic vagal (parasympathetic) stimulation slowing the faster intrinsic rate (100 to 120 per minute) of the normal cardiac pacemaker, the sinoatrial node. Conversely, tachycardias (fear, exertion, etc.) are a result of sympathetic nervous system stimulation overriding the vagal effects. Consequently, the heart rate effect of anesthetics is largely related to their influence on the autonomic nervous system.[17]

Although there are relatively few published studies on the electrophysiologic effects of anesthetics in isolated tissues, as a general rule, anesthetics (general and local), with the exception of cyclopropane, slow atrial-ventricular conduction velocity.[17] Such an effect generally decreases the incidence of arrhythmias. Indeed, local anesthetics are used

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Supported in part by Research Career Development Award HL-31752, USPHS.

therapeutically for this effect. However, excessive sympathetic or parasympathetic stimulation, either as a result of central nervous system drug action or indirectly through hypercarbia induced by respiratory depression, may cause clinical arrhythmias during anesthesia. Again, with the exception of cyclopropane, most arrhythmias during anesthesia and surgery probably result from nonanesthetic reflex effects (tracheal intubation, surgical stimulation, etc.). The effect of beta-adrenergic stimulation on heart rate and rhythm, whether from sympathetic nerve stimulation or administration of a beta-adrenergic drug, is dose related. As the dose (or intensity of stimulation) is increased, first sinus tachycardia, then ventricular premature contractions, ventricular tachycardia, and finally ventricular fibrillation result. There is a definite effect of anesthetics (particularly inhalation agents) on the dose of adrenergic drug necessary to produce these ventricular arrhythmias when compared with the awake or barbiturate-anesthetized animal. The dose of beta-adrenergic drugs necessary to produce ventricular arrhythmias is: (a) much lower during administration of cyclopropane, chloroform, and trichloroethylene: (b) somewhat lower during halothane (Fluothane inhalation); (c) and slightly or not at all decreased by anesthesia with methoxyflurane (Penthrane), fluroxene (Fluromar), diethylether, enflurane, (Ethrane), and isoflurane (Forane).[15, 17] Clinically, this means that beta-adrenergic drugs should usually not be used during anesthesia with the drugs mentioned in category (a) above, and cautiously with the drug in category (b).

MEASUREMENT OF VENTRICULAR FUNCTION

Measuring cardiac muscle function is relatively straightforward in an isolated strip of papillary muscle. It is possible to precisely control the predominant influences on the contractile performance of such a preparation:[39] (1) The initial length from which the muscle begins to contract (preload) is kept constant. (2) The amount of weight the muscle must pull against (afterload) can be accurately regulated. (3) The rate of contraction is produced by electrical stimulation. (4) The environment in which the muscle functions (the fluid in the bathing medium) can be precisely controlled. Consequently, the only variable is the contractile function of the muscle. As heart preparations being investigated become more like the intact heart in an intact animal, control of these important influences on contractile performance becomes more and more difficult. In man, such control is usually impossible.

However, knowing what the effects of preload, afterload, and rate of contraction are from the data in simpler systems, we are equipped to record the equivalent in vivo measurements when heart function is being investigated. The best estimate of preload is probably a combination of end-diastolic ventricular volume and pressure, but these are both difficult to measure in the left ventricle of man. Recently, measurement of "pulmonary capillary wedge pressure" with a balloon catheter in the pulmonary artery has given a reasonable approximation of end-diastolic pressure in the left ventricle.[48] However, most studies in man have

measured only right atrial or central venous pressure as an estimate of preload and this of course refers to the right ventricle, not the left.[37] Afterload is an easier measurement to make in man. Aortic (or less precisely, arterial) diastolic or mean blood pressures are relatively good estimates—Heart rate recording is relatively simple. Until recently, the environment in which the intact heart was functioning was not often considered. As was the case with the effects on heart rate and rhythm, autonomic nervous system influence is a most important consideration here as well. The oxygen tension and pH of the fluid perfusing the intact heart (arterial blood) should also be taken into account. In addition, there should be minimal or no effects from drugs other than the one which is being investigated. Few studies of the effects of anesthetics on ventricular function in man have controlled or measured all of the above factors. Consequently, imperfect studies must be considered with the realization that the information may not be precise.

In addition to the problem of the influences other than that of the drug in question on ventricular function, quantitation itself is a considerable task. (The author intentionally avoids the phrase "myocardial contractility" because of controversy over its meaning and measurement.) In the isolated muscle preparation, several measures of function of the contractile element can be made (Fig. 1).[37] If contraction is isometric (no

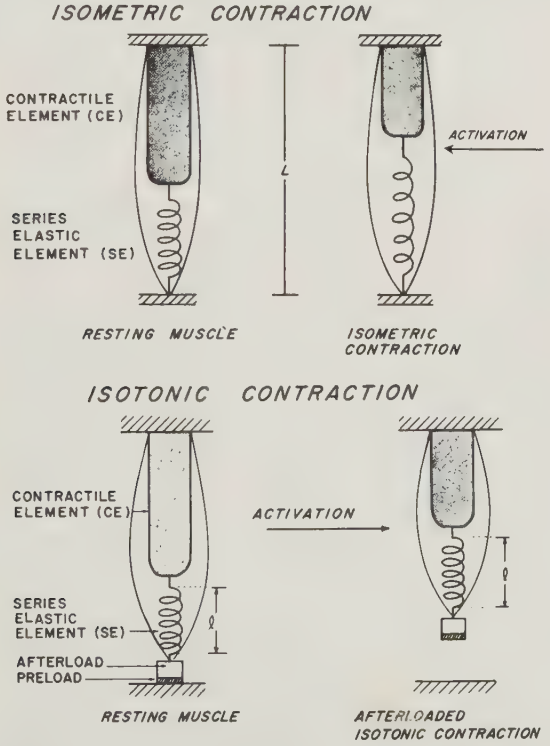

Figure 1. Models of cardiac muscle mechanics. (Reproduced from Shimosato, S., and Etsten, B. E.: Effects of anesthetic drugs on the heart; a critical review of myocardial contractility and its relation to hemodynamics. Clin. Anesth., 3:17–72, 1969. Used with permission.)

shortening, only tension being developed) the rate of rise of tension and the peak tension can be measured. If contraction is isotonic (afterload moved, muscle shortens, and work is performed) the velocity of shortening can be measured as well as the work and power developed. The most precise estimate of contractile function in the isolated muscle preparation is the plot of velocity of shortening versus the afterload moved, or the force-velocity curve. As afterload increases, the velocity of shortening decreases and vice versa. At 0 afterload, velocity is maximal (V_{max}). Conversely, at 0 velocity, force is maximal F_{max}. V_{max} can never be measured because even a single cardiac muscle sarcomere operates under some intrinsic force or load. It is likely that the published values for the extrapolated V_{max} are subject to rather wide errors and that the maximum velocity of shortening at the *lowest measured* afterload is more precise. Developed isometric tension can be measured with some degree of precision both in vitro and in vivo with a strain gauge arch sewn to the epicardial surface of the ventricle. Although it would appear that this method is applicable only to laboratory animals, such measurements have, in fact, been reported in evaluating the effects of various interventions, including anesthetics, on patients during surgery (see below).

Inasmuch as the rate of rise of tension in isolated muscle (dT/dt) is one estimate of contractile performance of isolated muscle, attempts have been made to use the rate of rise of intraventricular pressure (dP/dt) as an in vivo method. With high-fidelity recording equipment left ventricular dP/dt does indeed reflect contractile performance of the heart. However, it is sensitive to both preload and afterload.[27] Several manipulations have been made in an attempt to decrease this load dependence. If the maximal dP/dt (referred to as dP/dt henceforth) before the aortic valve opens (isovolumic) is related to the pressure within the ventricle at that precise moment, load dependence decreases markedly. A similar treatment relates dP/dt to the highest common developed pressure during two different states which are being compared in this same animal (CPIP) (Fig. 2).[27] Finally, an "in vivo" V_{max} estimate has been made by plotting dP/dt over IP during isovolumic contraction against the pressure in the ventricle and then extrapolating the downslope of the curve to 0 pressure (see the "in vivo" force velocity curve in Fig. 3). It is evident that the long extrapolation is subject to considerable error. Although there is some evidence that the extrapolated "V_{max}" is less load dependent than the dP/dt/IP, the latter measurement is easier, more accurate, and probably as useful.

These measurements involve left ventricular catheterization, which is not without some hazard to patients. Catheters in the aorta are less traumatic, albeit still "invasive." Some centers have used central aortic pressure-wave-form analysis to estimate ventricular function and cardiac output,[13a] although there are theoretical and practical problems with this approach. The development of catheter-tip flowmeters has allowed the measurement of aortic blood flow velocity in man and more importantly, aortic blood flow acceleration which is the rate of rise of the velocity or dV/dt. Again, this measurement is said to be independent of preload and afterload, although some doubt has been raised concerning this.[5]

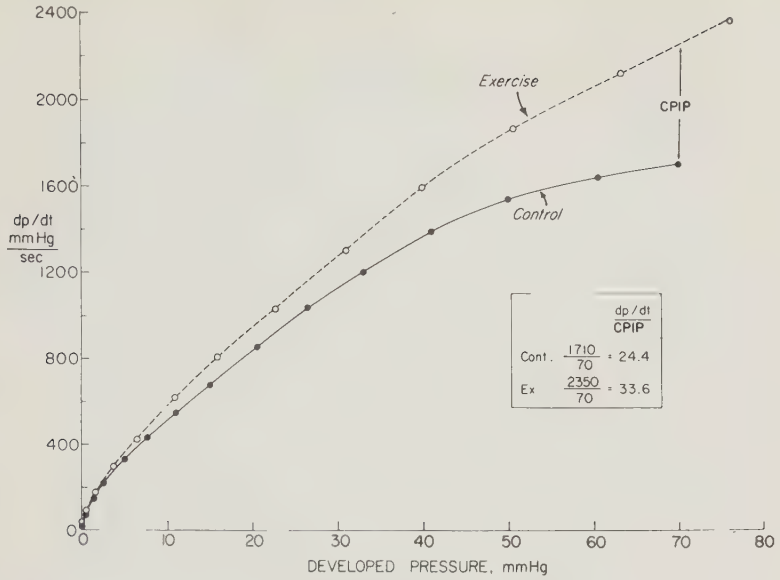

Figure 2. Common Peak Intraventricular Pressure. (Reproduced from Mason, D. T.: Usefulness and limitations of the rate of rise of intraventricular pressure (dP/dt) on the evaluation of myocardial contractility in man. Am. J. Cardiol., 23:516–527, 1969. Used with permission.)

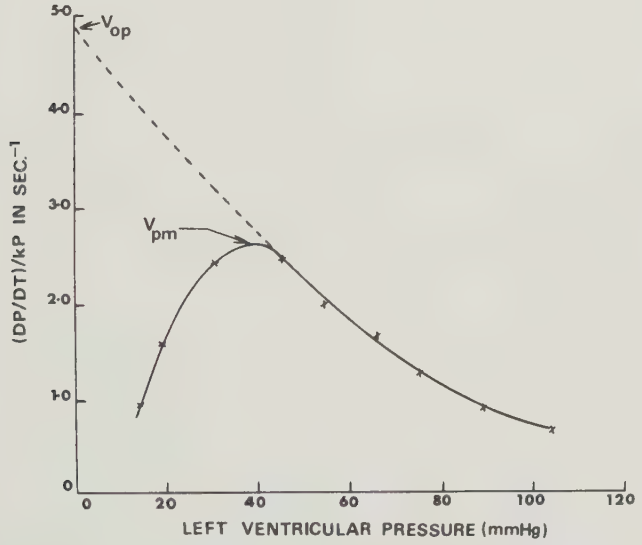

Figure 3. "In-vivo force-velocity curve." $V_{op} = V_{max}$, $V_{pm} = dP/dt/IP$. (Reproduced from Mirsky, I., Ellison, R. G., and Hugenholtz, P. G.: Assessment of myocardial contractility in children and young adults from ventricular pressure recordings. Am. J. Cardiol., 27:359, 1971. Used with permission.)

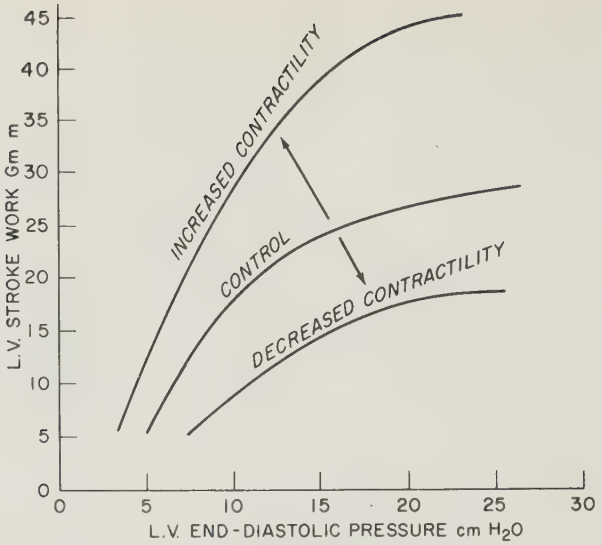

Figure 4. Ventricular function curves.

The most common invasive method for estimating ventricular function is the measurement of cardiac output. With either of the commonly used methods, (indicator-dilution or the Fick method), arterial and central catheters are necessary. Recently, the thermodilution technique has been popular where cold saline is used as the indicator and dilution measured by temperature changes in the bloodstream distal to the site of saline injection. In this technique, only one catheter is necessary with the proximal injection port in the right atrium or vena cava and the sensing thermister in the pulmonary artery. Catheter-tipped elements for measuring oxygen saturation and the dilution of green dye injected in a manner similar to the cold saline are also being evaluated for the clinical measurement of cardiac output.[52]

The dependence of cardiac output on a variety of noncardiac events, particularly venous return, is well known.[34] Consequently, if cardiac output is to be used as an estimate of ventricular function, preload and afterload should be measured and/or manipulated. The ventricular function curves advocated nearly 20 years ago by Sarnoff are a good example of this principle (Fig. 4).[35] Here the effect of increasing preload (or stretching diastolic muscle fiber length) on some aspect of ventricular function is plotted. Sarnoff used ventricular end-diastolic pressure as a measure of preload but subsequent investigators have been less precise, using right atrial or even central venous pressures. Although volume loading is a relatively simple method of manipulating a preload in isolated hearts or heart-lung preparations, it is considerably more difficult in man. Sarnoff chose an unfortunate measure of ventricular function for the vertical axis of his ventricular function curves, stroke work. Stroke work is the product of stroke volume and aortic pressure. Consequently, changes in aortic pressure (afterload) which may not be a result of changes in ventricular function will influence the function

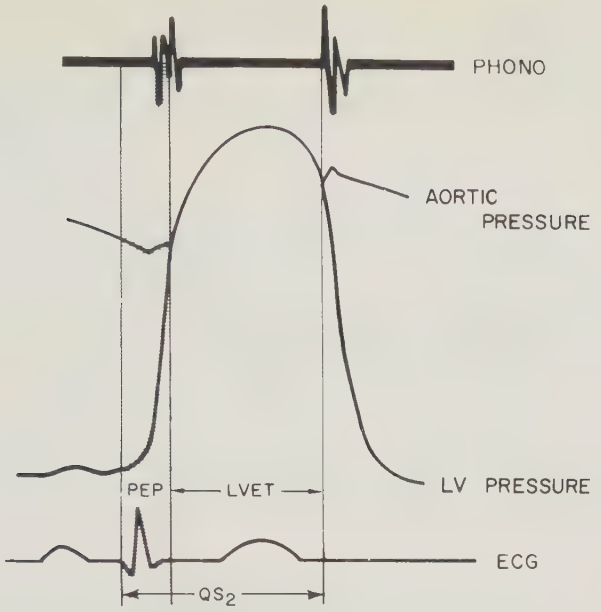

Figure 5. Systolic time intervals. *PEP* = pre-ejection period, *LVET* = left ventricular ejection time, QS_2 = electromechanical delay. (Reproduced from Weissler, A. M., Harris, W. S., and Schoenfeld, C. D.: Bedside techniques for the evaluation of ventricular function in man. Am. J. Cardiol., 23:577, 1969. Used with permission.)

curves as much as real changes in cardiac performance. In any event, an estimate of filling pressure and measurement of arterial pressure are essential if cardiac output or its derivatives are to provide quantification of ventricular function.

Methods which do not involve cutting or puncturing the body surface (noninvasive) are more desirable for clinical investigation. The most widely used of these has been the systolic time intervals derived from a phonocardiogram (heart sounds), electrocardiogram, and an arterial pressure pulse tracing (Fig. 5).[54] The period between the initiation of electrical depolarization of the ventricle and the opening of the aortic valve, the pre-ejection period (PEP), is the time when dP/dt is maximal. The duration of PEP is inversely proportional to ventricular function. The duration of left ventricular ejection (LVET) is an imprecise reflection of the output of the ventricle, as it measures the time that the aortic valve is open and the ventricle is actually pumping blood. Ventricular performance is directly proportional to this time interval. Since systolic time intervals are influenced by both preload and afterload, these should be measured, necessitating a central venous catheter at least.

Some of the best estimates of the effects of anesthetics on human heart function have used the ballistocardiogram (BCG).[9, 10, 42, 46] This technically demanding but noninvasive technique measures the displacement of the body caused by ejection of blood from the ventricles into the pulmonary artery and aorta[34] (Fig. 6). The I-J wave of the BCG has been shown to parallel dP/dt and aortic acceleration. Other less well docu-

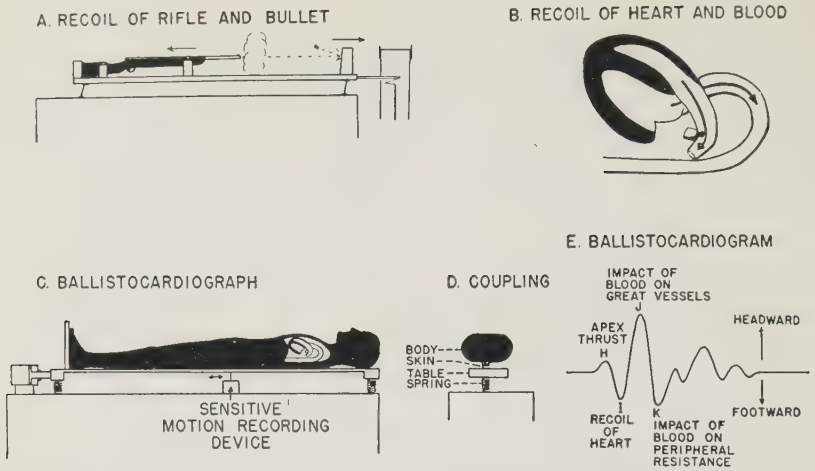

Figure 6. Principle and application of the ballistocardiograph. (Reproduced from Rushmer, R. F.: Structure and Function of the Cardiovascular System. Philadelphia, W. B. Saunders Co., 1972.)

mented noninvasive methods include changes in electrical impedance of the thorax, and airway pressures (pneumocardiogram).

As yet, all estimates of ventricular function in man (with the possible exception of the strain gauge arch) require concomitant measurement of preload, afterload, heart rate, and blood gases for any pretense of precision. It is little wonder that there are few really authoritative studies available.

EFFECTS OF INHALATION ANESTHETICS ON VENTRICULAR FUNCTION

Although all potent anesthetics depress cardiac function in vitro (muscle strips or perfused heart), several have minimal depressant actions in the intact animal and man. These "Group 1" anesthetics which include diethylether, cyclopropane, and fluroxene appear to produce sympathetic nervous system stimulation which counteracts the direct depressant effects of the drug.[40] "Group 2" anesthetics (halothane, methoxyflurane, enflurane, isoflurane, chloroform) on the other hand, produce a dose-related depressant effect on ventricular function in the intact animal.[41] However, in light planes of surgical anesthesia, depression is usually minimal, probably as a result of some degree of sympathetic activity.

Diethylether

The combination of minimal depressant effects on respiration and circulation has enabled diethylether to survive for more than 125 years as a clinically useful anesthetic drug. Although some studies have shown depression of stroke volume,[16] others, where arterial blood pressure was not decreased,[9, 21] have demonstrated very little effect of

diethylether on ventricular function. The importance of this relationship was shown by the demonstration that a severely depressed ventricular function curve produced by deep ether anesthesia in the dog could be returned to control levels merely by elevating the arterial blood pressure with a balloon catheter.[11]

Cyclopropane

Unlike diethylether, cyclopropane usually maintains or even elevates arterial blood pressure in deep levels of anesthesia. Partly as a consequence of this, clinical studies with the drug have shown no decrease in ventricular function as estimated by stroke volume measurements.[9]

Fluroxene

This halogenated ether behaves much like diethylether, although even with arterial hypotension during deep anesthesia, cardiac output has been shown to increase. In addition, BCG-IJ wave amplitude was unchanged, although the increase in heart rate could have been partly responsible.[9]

Halothane

All published studies with this most popular and widely studied of the inhalation anesthetics have shown dose-related hypotension and depression of ventricular function.[2, 9, 26, 32] The latter slowly recovers as duration of anesthesia is prolonged, although the mechanism remains obscure.[32] However, the only direct measure of ventricular function, the I-J wave amplitude of the BCG, did not recover like cardiac output.[9] Two remarkable studies were published in 1961 documenting dose-related depression in isometric tension developed by the human heart during halothane anesthesia. These studies used the strain gauge arch sewn to the epicardial surface of the right ventricles of patients during cardiopulmonary bypass[2] or pulmonary surgery.[26] Elevating the depressed arterial blood pressure during halothane anesthesia does not reverse ventricular function depression as is the case with diethylether, indicating that the cardiac depression is an important part of the mechanism of this hypotension.[11]

Methoxyflurane, Enflurane, Isoflurane

Unlike the other ethers, these anesthetics appear to depress ventricular function in a dose-related fashion, although there are good data only in dogs for methoxyflurane[30] and enflurane.[1] There is some evidence that isoflurane does not produce as much depression as the other drugs (and halothane) but the exact relationship remains unclear.[46]

Nitrous Oxide

For decades, this commonly used inhalation analgesic gas has been thought to have little or no effect on cardiac function. However, recent studies have demonstrated that nitrous oxide produces significant depression in ventricular function in as low a concentration as 40 per

cent.[10] In addition, depression of cardiac function has been demonstrated when the gas was added to morphine anesthesia.[56] When nitrous oxide is added to more potent inhalation anesthetics, there appears to be vasoconstriction, with increases in arterial blood pressure and peripheral vascular resistance.[42] Consequently, although the use of nitrous oxide with more potent drugs reduces the dose of the latter necessary for surgical anesthesia, it appears that the effect of nitrous oxide on cardiovascular function must be considered.

EFFECTS OF INTRAVENOUS ANESTHETICS ON VENTRICULAR FUNCTION

Although numerous intravenous drugs have been used for over a century to produce sleep and analgesia in man and anesthesia in animals, until recently no one drug could be used predictably and safely for surgical anesthesia in patients. During the last decade, the narcotic analgesics, particularly morphine in large doses, and new drugs such as ketamine and the steroid combination, althesin, have been used alone in selected patients for surgical anesthesia. However, the intravenous drugs are still used mainly as specific adjuvants for induction, analgesia, muscle relaxation, etc., in addition to other drugs.

Hypnotics for Induction

The time tested and most popular of this group of drugs are the barbiturates. The "ultrashort-acting" drugs (thiamylal, thiopental, methohexital) all appear to have much the same effect on the heart. Early work suggested that most of the depression of cardiac output seen with these drugs resulted from venodilation and decreased venous return to the heart producing inadequate diastolic filling. More recent data using systolic time intervals[22] and left ventricular dP/dt in man[36, 43] have shown significant depression in ventricular function.

Diazepam (Valium) has been very popular both for premedication and as an anesthetic adjuvant in recent years. Low doses (0.13 mg per kg) produced little effect on cardiac output,[7] while large doses (0.77 mg per kg) were shown to result in a 30 per cent decrease in stroke volume in healthy patients.[33]

Intravenous drugs not available in the United States include propanidid, althesin, and etomidate.

Propanidid is a eugenol derivative which has been in widespread use in Europe for 10 years as an induction agent. Recent data in man have indicated that it produces significantly more depression in ventricular function than the barbiturates,[36, 43] and its popularity is declining at the present time.

There has been a great deal of experimental work in Europe on althesin, an hypnotic which is a combination of synthetic steroid compounds. It appears to have effects on ventricular function similar to the barbiturates, producing perhaps slightly more tachycardia.[45]

Etomidate is an imidazol-carboxyl ester, the latest of the new intravenous hypnotic drugs being investigated. Preliminary data in animals and man indicate that it has the least cardiac depressant effect of any of the induction agents tested;[18] however, it must be used with other drugs because of a significant incidence of excessive muscle activity in man. Consequently, its future remains uncertain.

Narcotic Analgesics

Widespread use of morphine in patients with cardiac disease followed the initial study of Lowenstein et al.[25] This showed little effect of 1 to 2 mg per kg of intravenous morphine on cardiac output in normal patients and an increase in cardiac output with 0.5 to 1.0 mg per kg in patients with valvular heart disease. Other studies have supported the original findings,[56] although extracardiac effects, particularly peripheral vasodilation, have produced alarming hypotension in hypovolemic patients. Tachycardia and hypertension have also been seen which have been disturbing in patients with ischemic heart disease.

As each new synthetic narcotic has been produced, claims have been made for superior properties compared to the other opiates. There have been no convincing studies in man showing any major difference in the effect of these drugs on cardiac function from the oldest of the group, meperidine, through the newer drugs such as fentanyl and phenoperidine. In dogs, fentanyl has been shown to produce significantly less depression in cardiac function than meperidine,[13] but great caution must be used in transferring the effects of intravenous anesthetics on animals to patients.

Dissociative Drugs

Ketamine is a "dissociative" anesthetic whose popularity has increased due to the lack of cardiovascular depression. Although the drug produces dose-related depression in cardiac muscle function in isolated systems,[8] studies in man have shown increases in heart rate, cardiac output, and left ventricular pressure derivatives.[50, 51, 53] The best of the published studies on the effect of ketamine on ventricular function in man have come from Tweed and co-workers.[50, 51] They used catheter-tipped micromanometers placed in the left ventricle of patients at the time of cardiac catheterization and paced the hearts to compare control and drug effects. They showed that stroke volume and the CPIP index, as well as extrapolated V_{max}, increased significantly after 2 mg per kg of ketamine intravenously (Fig. 7).

Combinations of central tranquilizing drugs, such as droperidol, and narcotics, such as fentanyl have been termed "neurolept anesthesia." Droperidol and fentanyl are combined as Innovar. As yet no other combinations are available in the United States. Droperidol has been shown to have little effect in one study[20] and in another, to increase ventricular performance.[44] It increased heart rate and cardiac output, but fentanyl restored these changes to awake control levels.[44] Neurolept anesthesia has been especially popular for high risk cardiac patients, although objective data in this group are still scant.

Neuromuscular Blocking Drugs

Safe anesthesia for high-risk patients has depended to a large extent on the use of this class of drugs to avoid high doses of central nervous system depressing drugs. Although it is difficult to measure the effects of these drugs by themselves (for obvious ethical reasons), all available studies have shown that none of the commonly employed agents (suc-

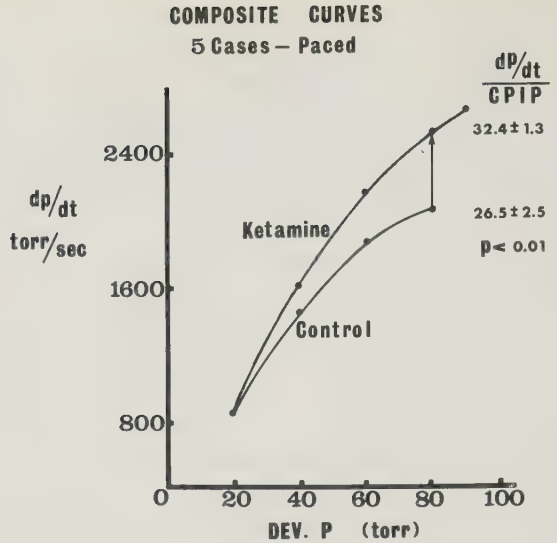

Figure 7. Effect of ketamine (2 mg per kg) on common peak intraventricular pressure (CPIP) in man. (With kind permission of W. Arnold Tweed, M.D.)

cinylcholine, d-tubocurare,[23] pancuronium,[47] and gallamine[24]) have an appreciable effect on ventricular function. Two of these investigations employed the strain gauge arch sewn to the epicardium of patients during cardiopulmonary bypass.[23, 24] Succinylcholine can produce bradycardia and/or ventricular arrhythmias, particularly in association with hyperkalemia[19] and disease states with marked tissue wasting (burns,[49] paraplegia, and other neurologic diseases,[6] and massive trauma[4]). D-tubocurare tends to produce bradycardia and hypotension,[23] while gallamine[24] and pancuronium[47] generally cause an increase in heart rate and little change in arterial blood pressure.

LOCAL AND REGIONAL ANESTHESIA

Local anesthetics, particularly lidocaine, have been extensively used for their anti-arrhythmic effects. Although abolition of ventricular arrhythmias can generally be achieved with doses that do not affect ventricular function, higher doses of all local anesthetic drugs will produce progressive decreases in cardiac output (as well as interfering with atrioventricular conduction). Consequently, when the effects of local anesthetic nerve blocks on ventricular function are measured, the possibility of the systemic effects of the drugs used must be considered. For major nerve blocks where large volumes of relatively concentrated local anesthesia are necessary (brachial plexus and epidural), such effects are certainly possible. However, if advice concerning maximum allowable dosage is heeded and care is taken to avoid intravascular injection, the systemic effects are minimal. On the other hand, when epinephrine is included in the local anesthetic solution, there may be significant tachy-

cardia, hypotension, and increase in cardiac output resulting from beta-adrenergic effects.[3] In healthy, well-hydrated patients, the effects of epidural or spinal anesthesia as high as the second thoracic dermatome level have been shown to have little or no effect on cardiovascular function as measured by several investigators.[3, 38]

MYOCARDIAL (CORONARY) BLOOD FLOW AND OXYGENATION

The measurement of coronary artery blood flow and myocardial oxygen consumption is both invasive and difficult. As a result, there have been few studies of the effects of anesthetics in animals and even fewer investigations in man. Interestingly, the earliest study was in man, where a 50 per cent decrease in both arterial pressure and coronary blood flow was shown after spinal anesthesia in a group of patients.[14] Because calculated cardiac work fell as much as coronary blood flow, and since there were no changes in oxygen or lactate extraction, the investigators felt that the fall in coronary blood flow was in response to decreased oxygen demands of the heart. They concluded that myocardial oxygenation was adequate. Not until 1972 was another study in humans published on this subject.[44] During the last 2 years, one multidepartmental team has published a series of reports on the effects of several intravenous drugs including ketamine, droperidol-fentanyl, and althesin on myocardial blood flow and metabolism in man.[18, 36, 44, 45] In general, they found that coronary blood flow and oxygen consumption paralleled changes in cardiovascular function. Animal studies on inhalation anesthetics over the last 5 years have shown the same results.[29] Where cardiac function was maintained or increased (diethylether and cyclopropane). so were coronary blood flow and myocardial oxygen consumption. If the anesthetics depressed cardiac function (halothane, methoxyflurane, and fluroxene), perfusion and oxygenation of the heart decreased accordingly. In all cases, analysis of lactate and oxygen extraction suggested that there was adequate myocardial tissue oxygenation.

These results pose an interesting problem. Generally, the assumption has been made that anesthetic depression of cardiac function is an undesirable pharmacologic property. If this depression in function is accompanied by an equivalent (or perhaps even greater) decrease in myocardial oxygen demand, perhaps the effect might be beneficial. For example, patients with coronary artery disease are treated with antianginal drugs such as propranolol and the nitrates in order to decrease myocardial oxygen demand.[28] Of course, too great a decrease in arterial blood pressure can lead to decreased coronary blood flow and oxygen delivery as a primary effect. Nevertheless, moderate cardiac depression by a drug like halothane may be more beneficial to the patient with ischemic heart disease than hypertension and tachycardia produced by a drug such as ketamine. This is a subject that requires further investigation.

SUMMARY

In man, high doses of the "group 1" inhalation anesthetics (diethylether, cyclopropane, and fluroxene) produce relatively minor depression of ventricular function, although it is possible to depress the heart if the dose is great enough. The "group 2" drugs (halothane, methoxyflurane, etc.) produce dose-related depression in cardiac function, but reasonable cardiac outputs and blood pressure can be maintained at light anesthetic levels. Much the same can also be said for the intravenous barbiturates and other hypnotics. If ventilation is supported and hypovolemia avoided, large doses of the narcotic analgesics appear to produce minimal cardiac effects. The only intravenous drug which stimulates the heart is the dissociative anesthetic ketamine, and this is probably an autonomic, reflex phenomenon (as with group 1 inhalation anesthetics). Regional anesthesia and the neuromuscular blocking drugs appear to have relatively little effect on ventricular function.

Most of the work in man on the effect of anesthetics has been in healthy patients or volunteers. The effects on patients with severe heart or other systemic disease may well be different. In fact, low concentrations of fluroxene have been shown to produce significant depression of stroke volume in patients with aortic valvular disease[55] in contrast to the effects on healthy volunteers.[9] All potent central nervous system depressant drugs possess the potential for significant cardiac depression. If such depression is undesirable in a particular patient, the only safe way to administer anesthesia is by careful titration of the dose against the best measurement of cardiac function which is available. At the present time, this would mean measuring at least direct arterial pressure, central venous pressure, and a continuous electrocardiogram. The optimal management would probably include recording systolic time intervals, pulmonary capillary wedge pressure, and some measure of cardiac output as well. All the skill and pharmacologic knowledge available cannot substitute for vigilant monitoring and careful titration of drug dose in the clinical situation.

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Effects of Anesthetics on the Kidney

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Anesthetic effects on renal function have been given considerable attention since the report of Pringle and co-workers in 1905[23] who observed a marked reduction in volume and nitrogenous content of urine during and after diethyl ether anesthesia. With the introduction of methods for quantification of the various aspects of renal function, numerous studies of anesthetic effects on the kidney have been reported. In order to better understand these studies a brief review of normal anatomy and physiology of the kidney will be presented. A presentation of the effects of preanesthetic drugs and general and regional anesthetics will be covered in this review, as well as a discussion of the undesirable nephrotoxic properties of some general anesthetics.

ANATOMY AND PHYSIOLOGY OF THE RENAL CIRCULATION

Anatomy

The basic unit of the kidney, the nephron, is a complex vascular-tubular network. Each kidney has 1 to 1.5 million nephrons. The blood supply of the kidney comes via the renal artery, which, on entering the kidneys, divides into interlobar branches. These branches bend over the base of the medullary pyramid to form the arcuates and run toward the periphery in the cortex. In their course they give rise to short lateral branches, the afferent arterioles, each of which supplies one or more nephrons. On entering Bowman's capsule, an afferent arteriole expands and branches into several trunks, which subdivide into capillary loops. These loops convene to form an efferent arteriole, whose branches descend and ascend, following the tubular portions of the nephron as the vasa recta. These in turn reassemble to form a venule, which enters an interlobular vein. The venous drainage thereafter parallels the arterial supply to the kidney.[25]

Smooth muscle surrounds the afferent and efferent arterioles, and by its contraction can alter resistance to the flow of blood through the

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glomerular capillaries and the postglomerular peritubular capillaries formed from the efferent arteriole. As the afferent arteriole enters Bowman's capsule, the media and adventitia are modified to form a perivascular cuff of cells with polychromatic granules of renin that stain with fuchsin. These are referred to as the juxtaglomerular cells and are believed by some to play a role in regulation of renal circulation.

Innervation of the kidney is derived from the thoracolumbar sympathetic nerves T4 to L4. No functional parasympathetic innervation of the kidney has been demonstrated. Visceral efferent nerves follow the renal vessels to their terminations in smooth muscles of the arterioles to the nephron. Visceral afferents from the capsule of the kidney travel with the sympathetic efferent nerves.

Physiology

For many years, renal hemodynamics were thought to depend solely on the head of arterial pressure delivered to the kidney. It is now known that renal blood flow does not change proportionately with pressure in the range from 70 to 200 torr, and that the glomerular filtration rate does not respond to pressure changes as a simple filtration process. Work with isolated kidneys has revealed that an intrinsic property of the kidney that is not related to external nervous or hormonal control is responsible for this autoregulation of renal blood flow. Three theories have been proposed to explain autoregulation of renal blood flow and glomerular filtration rate.

MYOGENIC THEORY. This proposes that smooth muscle of arterioles responds to pressure changes, thereby changing resistance and controlling flow. Autoregulation may be abolished by infusion of procaine and papaverine into the renal artery in amounts sufficient to relax the smooth muscle of the arterioles. Tobian[28] and Britton[2] have suggested that the juxtaglomerular apparatus plays an important role in the autoregulation of renal circulation via the renin-angiotensin mechanism.

CELL SEPARATION THEORY. This theory suggests that changes in viscosity of blood within the kidney causes separation of plasma and cells in response to changes in arterial pressure and results in autoregulation of renal circulation. Little evidence of support has been presented.

INTRARENAL PRESSURE THEORY. According to this theory, increased arterial pressure is accompanied by raised renal interstitial pressure, which acts to increase resistance to flow through the kidney. Few investigators have accepted this theory.

In addition to autoregulation of flow under normal conditions, extrarenal neural influence may affect renal blood flow when there is hypotension below the autoregulatory range. Further, factors such as increased ureteral pressure are known to affect renal blood flow.

In general, it is accepted that renal blood flow is regulated to produce a constant rate of glomerular filtration by maintaining filtration pressure. In emergencies, as in severe hypotension, the 20 to 25 per cent of the cardiac output that normally goes to the kidney may be largely diverted to the heart and brain.

Measurement of Renal Hemodynamics in Man

RENAL BLOOD FLOW. Measurements of renal blood flow (RBF) before and during anesthesia have made use of the plasma clearance of

paraaminohippurate (PAH). PAH is infused at a constant rate, removed by the proximal tubules, and excreted into the urine. Assumptions made in this method are as follows: (1) all the PAH is removed from the kidney as blood travels from the renal artery to the renal vein; (2) PAH is neither synthesized, destroyed, nor altered by the kidney; (3) PAH does not alter renal hemodynamics; and (4) all PAH removed from plasma is excreted into the urine and collected. Since, by the Fick principle, the quantity of substance removed by the organ is equal to the quantity delivered in arterial blood less the quantity leaving in venous blood, one can write

$$(A)\ Qu = TRBF \times A \times u - TRBF \times R \times u$$

where Qu = quantity of indicator substance removed by kidney in time period u; $TRBF$ = total renal blood flow (m1 per min); A = arterial concconcentration; and R = renal venous concentration. Assuming u can be 1, equation (A) can be rewritten:

$$(B)\ TRBF = \frac{Q}{A - R}$$

but

$$(C)\ Q = UV$$

where U = urinary concentration of indicator and V = urinary volume (ml).

By assumption (1) R = O, therefore

$$(D)\ TRBF = \frac{UV}{A}$$

In practice, the level of PAH in arterial blood is assumed to be the same as that in peripheral venous blood, since no other organ but the kidney extracts PAH from blood. Changes are measured at successive time intervals. PAH is carried only in the plasma, and so one therefore obtains plasma clearance of PAH by measuring PAH concentration in peripheral venous plasma and urine, and urinary volume.

Normal PAH plasma clearance is 660 ml ± 15 per cent per minute per 1.73 m^2 body surface area. By determining the hematocrit (HCT), one can calculate the renal blood flow.

$$RBF = RPF \times \frac{1}{1 - HCT}$$

where RPF = renal plasma flow

Renal extraction of PAH determined by renal vein catheterization is 90 per cent, or 0.90, under normal conditions. The remaining 10 per cent of RBF is assumed to supply the nonactively secreting areas of the kidney, such as the capsule, pelvis, and perirenal fat. Renal blood flow determined by PAH clearance is therefore referred to as effective renal blood flow.

Factors that invalidate the clearance method are: (1) Oliguria or marked fluctuations in urine flow. In this instance, collected samples do not reflect true excretion. (2) Rapid changes in plasma concentration that prevent establishment of equilibrium among blood, interstitial fluid, and tubular urine.

Evidence has been presented by Goldberg,[13] Balint,[1] and Selkurt[24] indicating that at low urine volumes (less than 1 ml per min), discrepancies are observed between renal blood flow measured by clearance techniques and direct measurement or an indirect Fick technique using radioactive krypton. In these studies, PAH appeared to be stored without a change in its extraction.

INTRARENAL DISTRIBUTION OF BLOOD FLOW. By means of injection of a saline solution of inert radioactive gas such as krypton or xenon into the renal artery, and monitoring externally by a scintillation counter, one obtains a washout curve of the radioactivity.[27] This can be analyzed as the sum of four exponential functions, and rates of blood flow from the cortex, outer and inner medulla, and perirenal fat can be obtained.

GLOMERULAR FILTRATION RATE. The glomerular filtration rate (GFR), like renal blood flow, is based on the plasma clearance of an inert substance. Inulin, a fructose polysaccharide, is freely filtered through the glomerular capillary membrane and is neither reabsorbed nor secreted by the renal tubules.

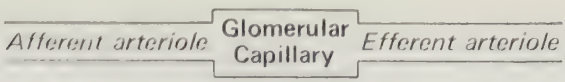
$$GFR = \frac{U_I V}{P_I}$$

where GFR = glomerular filtration rate (ml per min); U_I = inulin concentration in urine; V = urine volume (ml per min); P_I = inulin concentration in plasma. In man, glomerular filtration is 125 ml per 1.73 m^2.

Classically, the ratio of glomerular filtration rate and renal plasma flow is expressed as the filtration fraction (FF). Changes in the caliber of the afferent and the efferent arterioles are reflected in changes of this ratio. Afferent arteriolar constriction reduces glomerular filtration and pressure and filtration rate more than renal plasma flow. A decrease in FF is calculated in this instance. Efferent arteriolar constriction increases glomerular pressure, while renal plasma flow is reduced to a great degree. This is reflected as an increase in the FF (Fig. 1).

WATER EXCRETION. Water is excreted in the urine in two forms: (1) water associated with the osmotically active solutes and (2) solute-free water. By determining the osmolality (total solute concentration in mOsm per kg) of urine and serum by freezing point depression, one can calculate the osmolar clearance (Cosm), or water associated with osmotically active solutes. By substracting Cosm from the total urine volume (V) one obtains the solute-free water C_{H_2O}, a quantitative expression of urinary dilution. If V is small and concentrated, a negative free water clearance (T_{CH_2O}) is obtained. This represents the water reabsorbed by the renal tubules to produce this concentrated urine and is a quantitative expression of urinary concentration.

$$FF = \frac{C_{IN}}{C_{PAH}}$$



Afferent arteriolar constriction →Decreased glomerular pressure
FF decreased with reduced C_{PAH}
Efferent arteriolar constriction →Increased glomerular pressure
FF increased with reduced C_{PAH}

Figure 1. FF = filtration fraction, C_{IN} = inulin clearance, C_{PAH} = PAH clearance.

EFFECTS OF PREANESTHETIC DRUGS ON RENAL FUNCTION

Narcotics and barbiturates, the most commonly employed drugs for preanesthetic sedation, have small effects on the kidney when administered in their usual clinical dosage.[21] Morphine, meperidine, and other narcotics that have been studied, produce a small reduction in glomerular filtration rate, urine volume, and urinary solute excretion without resulting in increased urinary concentration. Secobarbital and other barbiturates produce similar effects. The reduction in urinary volume and urinary solute excretion has been explained on the basis of reduction in GFR. The absence of urinary concentration following administration of these drugs in man suggests their inability to stimulate the secretion of antidiuretic hormone (ADH) under the conditions of these studies.

Phenothiazines such as promazine and chlorpromazine in therapeutic doses have been reported to increase volume and dilution of the urine, suggesting ADH suppression. Other sedatives such as chloral hydrate have little effect on renal function. Similarly, anticholingerics such as atropine and scopolamine, used for their drying effect on salivary and bronchial secretions, have little effect on renal function.

Whether or not drugs administered for preanesthetic medication or postoperatively to patients with preexisting renal disease, pain, dehydration, and translocation of fluid have more significant effects on renal function remains to be determined.

EFFECTS OF GENERAL ANESTHETICS

Without exception, induction of general anesthesia is associated with profound changes in renal hemodynamics, water, and electrolyte excretion.[21] This has been demonstrated in volunteer subjects in the absence of preanesthetic medication, and other variables known to affect renal function such as dehydration, pain, blood loss, abdominal packs, and retractors. The subjects were well hydrated, as their urine/serum osmolality (U/Posm) ratio was less than 1.

In one study anesthesia was induced with cyclopropane and ox-

ygen,[11] tracheal intubation facilitated by the administration of succinylcholine, and anesthesia maintained with cyclopropane and oxygen. Assistance or control of respiration was utilized to avoid hypoxemia and respiratory acidosis or alkalosis. Urine volume was markedly reduced; the positive free-water clearance was transformed into a negative free-water clearance; and the U/Posm ratio was increased. These changes were indicative of conversion from a diuresis to a marked antidiuretic state. GFR (inulin clearance) and ERPF (PAH clearance) were also significantly decreased. These changes persisted for prolonged periods of time.

Similar results have been demonstrated under analogous experimental conditions with halothane and oxygen[19] or thiopental, nitrous oxide, and oxygen with morphine and neuromuscular blocking drugs as administered clinically.[8] In other studies, fentanyl-nitrous oxide-oxygen, diethyl ether, and methoxyflurance anesthesia have been reported to produce similar effects. Increasing depth of anesthesia is apparently associated with more profound reductions in urinary volume and renal hemodynamics. Evidence for greater depression of renal function with increased depth of anesthesia and dehydration has been presented by others as well.[18] A summary of anesthetic effects on renal function is presented in Tables 1 and 2.

The mechanisms by which anesthetics are believed to affect water and electrolyte excretion include the renal hemodynamic changes observed, liberation of antidiuretic hormone, and possibly an aldosterone effect on the renal tubules secondary to activation of the renin-angiotensin system. With reduction in GFR one would expect reductions in water and electrolyte excretion. Administration of ethanol, a potent inhibitor of ADH but without effect on renal hemodynamics in the usual concentration administered, results in a reappearance of free water in the urine, an increased urinary volume, and return of U/Posm ratio to less than 1. This is indirect evidence indicating liberation of ADH during cyclopropane and halothane anesthesia. Ethanol administration delays,

Table 1. *Hemodynamic Changes in Renal Function during Anesthesia (Per Cent Changes from Control)*

AGENT	INULIN CLEARANCE (ml per min)*	PARA-AMINO-HIPPURATE (ml per min)*	FILTRATION FRACTION (C_{IN}/C_{PAH})†	RENAL VASCULAR RESISTANCE (mm Hg per L per min)	MEAN ARTERIAL PRESSURE (mm Hg)
Cyclopropane (19 vol. per cent)	−39	−42	+14	+84	+11
Halothane (1.5 per cent)	−19	−38	+39	+69	−8
N_2O-relaxant-narcotic:					
Premedications	−13	−8	−4	+20	+4
Anesthesia	−27	−36	+23	+61	−1

*Corrected to 1.73 m^2 body surface area.
†C_{IN} = Inulin clearance; C_{PAH} = Paraaminohippurate clearance.

Table 2. *Water and Electrolyte Excretion (Per Cent Changes from Control)*

AGENT	URINE VOLUME (ml per min)*	OSMOLALITY OF URINE (mOsm per kg)	URINE/ SERUM OSMOLALITY	OSMOLAR CLEARANCE (ml per min)*	FREE-WATER CLEARANCE (mm per min)*
Cyclopropane (19 vol. per cent)	−98	+611	+590	−86	−103
Halothane (1.5 per cent)	−91	+563	+583	−53	−106
N_2O-relaxant-narcotic:					
Premedication	−7	−1	0	−4	−10
Anesthesia	−59	+193	+267	−31	−71

*Corrected to 1.73 m^2 body surface area.

but does not completely reverse, the antidiuresis observed with nitrous oxide-relaxant anesthesia, suggesting a more intense stimulation of ADH release with this combination of drugs. Increased levels of ADH in the blood have been observed during ether and methoxyflurane anesthesia, providing direct evidence that ADH has a role in some of the alterations in renal function during general anesthesia.

Renal hemodynamic changes during general anesthesia may be explained in part on the basis of general hemodynamic effects observed with the individual agents. Cyclopropane, diethyl ether, thiopental, nitrous oxide, and neuromuscular blocking drugs are associated with increased sympathetic nervous activity. Stimulation of sympathetic nerves to the kidney has been observed to result in decreased GFR, decreased ERPF, and increased renal vascular resistance. Halothane and methoxyflurane are associated with reductions in GFR and ERPF. In order to explain the increased renal vascular resistance observed with halothane, an agent not usually associated with increased sympathetic nervous activity or peripheral vasoconstriction, a study of the renin-angiotensin system during anesthesia was carried out.[10] Increased levels of renin in peripheral blood were observed during both cyclopropane and halothane anesthesia, suggesting the possibility that angiotensin, a potent vasoconstrictor, may be partly responsible for the hemodynamic changes during use of these anesthetics. The possibility exists that combinations of vasoactive substances such as catecholamines, angiotensin, and ADH may affect the renal vasculature, producing the observed alterations.

General anesthetic effects are apparently transitory, returning to control levels after the patient emerges from anesthesia. What role, if any, anesthetics have in the production of permanent alterations in renal function, when accompanied by hemorrhage and other complications during operation, also remains to be determined. The effects of anesthetics on patients with preexisting renal disease remain to be determined.

REGIONAL ANESTHESIA AND RENAL FUNCTION

Changes in renal function with spinal and epidural anesthesia have been the subject of several studies. The results have been somewhat conflicting, the differences mainly being related to differences in experimental conditions.[7] Most studies indicate that in normal man, in the absence of surgical stimulation, reduction (12 per cent) in ERPF and no change in GFR or renal vascular resistance are observed at sensory levels of spinal anesthesia of T1 to T2, which produce complete renal sympathectomy. General systemic hemodynamic changes in these subjects include a small (10 per cent) increase in cardiac output and a reduction (20 per cent) in mean arterial pressure. These results suggest that the kidney is able to autoregulate blood flow to maintain the important function of glomerular filtration. Despite these minor hemodynamic changes, marked alterations in urinary volume and urinary concentration were observed. An 86 per cent reduction in urinary volume, with a marked increase in Cosm, and 70 per cent reduction in free-water clearance indicate a marked antidiuresis and suggests liberation of ADH during spinal anesthesia. No significant alterations of plasma renin were observed in these subjects.

A similar study of continuous epidural anesthesia to sensory levels of T1 to T2 with 1.3 per cent lidocaine and epinephrine (1:450,000) revealed a small (11 per cent) reduction in mean arterial pressure, a greater increase (25 per cent) in cardiac output, and no alteration of renal hemodynamics. These changes are probably related to the effects of catecholamines, or lidocaine, or both, absorbed from the epidural space. In contrast to spinal anesthesia, epidural anesthesia resulted in an increase in urinary volume and solute free water, suggesting suppression of ADH. This could be the result of a direct central nervous system effect of lidocaine.

ANESTHETIC DRUGS CAUSING RENAL DYSFUNCTION

Renal toxicity associated with histologic changes in the renal tubules have been described in numerous reports with the administration of chloroform, ethyl chloride, and divinyl ether. In 1966, two reports of high output renal failure following the administration of methoxyflurane for major operative procedures suggested that this anesthetic may be associated with renal dysfunction usually observed for 6 to 10 days postoperatively, but in a few instances persisting up to 29 months.[6,22] The characteristic picture observed was large urine volume (2.5 to 4 liters per day) with dehydration as evidenced by increased serum osmolality sodium, chloride, and increased blood urea nitrogen (BUN) levels. The urine had a fixed specific gravity with an osmolality close to that of serum. Fluid deprivation and vasopressin challenge failed to result in urinary concentration. With time the kidneys returned towards a normal response to fluid deprivation, vasopressin, and dilution testing.

Methoxyflurane has been found to be metabolized to both organic- and inorganic-fluoride-containing metabolites as well as oxalate.[16]

Polyuric renal failure following methoxyflurane anesthesia in obese patients has been correlated with elevated levels of these fluoride containing metabolites.[26] A high degree of oxalate precipitation in renal tubules and excretion into the urine has also been reported in patients in renal failure after methoxyflurane anesthesia.[12] A well-designed prospective study comparing groups of patients receiving methoxyflurane and oxygen vs. halothane and oxygen revealed significant differences in renal function between the two groups.[4] Postoperatively, six of the 12 who received methoxyflurane exibited polyuria with low specific gravity of the urine; hypernatremia; elevated serum osmolality, BUN, creatinine, and uric acid; and a decrease in uric acid clearance. The remaining six who recieved methoxyflurane had increased serum uric acid levels in the blood. Weight loss in the group which received methoxyflurane was significantly greater than in those who received halothane. Concentration and vasopressin infusion tests in those who exhibited polyuria following methoxyflurane revealed failure to concentrate urine normally. Those receiving halothane had no such abnormalities in renal function. The degree of renal dysfunction was correlated with level of inorganic fluoride levels in those who received methoxyflurane. A toxic effect of fluoride on the distal renal tubules was postulated as the cause of renal dysfunction.

An animal model simulating the picture observed in man supports the theory that elevated inorganic fluoride is the agent responsible for nephrotoxicity following methoxyflurane,[19] and that there is a dose-response relationship. Several reports without evidence of renal dysfunction involving brief exposures to low doses have appeared suggesting that its administration is not always associated with nephrotoxicity.[5, 15] It is convenient to think that large quantities of this very fat-soluble agent rapidly metabolized to fluoride-containing metabolites in obese patients for prolonged periods of time may be the ideal setting for development of renal dysfunction with this agent.

An association of tetracycline, a known renal nephrotoxin, and methoxyflurane in the production of renal failure has been observed. Polyuric renal failure was not the characteristic picture reported. Oliguric renal failure was more commonly observed in these patients.[17]

ANESTHESIA FOR PATIENTS IN RENAL FAILURE

Since it is possible to sustain patients in acute and chronic renal failure by means of dialysis, increasing numbers of these patients are presented for anesthesia and operation, including renal transplantation. Patients with chronic renal failure frequently have associated cardiovascular disease including hypertension, peri- and myocarditis, pleuritis with effusion, and marked biochemical disturbances including anemia, azotemia, hyponatremia, hyperkalemia, hyperphosphatemia, and metabolic acidosis. Hepatic function is frequently abnormal with resultant diminished ability to metabolize drugs. Evidence for reduced levels of cholinesterase in tissues including the heart and blood has also been reported.

These patients are extremely sensitive to the myocardial depressant effects of the potent inhalational anesthetics such as cyclopropane, halothane, and methoxyflurane, and will develop significant hypotension at moderate levels of anesthsia. Those poorly prepared for anesthesia and operation, as evidenced by hyperkalemia (serum potassium greater than 5.5 mEq per L) and metabolic acidosis, are more likely to develop myocardial depression and severe cardiac arrhythmias. Extremely light general anesthesia or regional anesthetic techniques such as continuous spinal or epidural anesthesia have been recommended for the management of these patients.[14, 29]

Neuromuscular blocking drugs have produced problems in these patients. Fatal cardiac arrest and/or severe arrhythmias have been reported following the administration of succinylcholine in patients with hyperkalemic renal insufficiency. Levels of serum potassium increasing to as much as 8.9 mEq per liter have been observed following succinylcholine administration to facilitate tracheal intubation in patients who start with elevated serum potassium. Careful monitoring of the EKG, adequate preparation to lower serum potassium, and the prior administration of a depolarizing neuromuscular blocking drug such as d-tubocurarine are recommended to alleviate or reduce this hazard. Avoidance of succinylcholine is not difficult, and perhaps preferable in hyperkalemic patients. Patients well controlled on hemodialysis with relatively normal serum sodium concentrations have not been found to have marked increases in serum K following succinylcholine.[20]

Drugs such as gallamine and decamethonium excreted only by the kidney, and not metabolized, have been found to produce prolonged neuromuscular blockade following their administration to patients with chronic renal failure. Repeated hemodialysis has been found necessary to treat this problem. These drugs are therefore not recommended for use in the presence of poor renal function.[3]

D-tubocurarine is largely metabolized in the liver and excreted into the bile, while only a small amount is excreted by the kidney. This accounts for the ability of the patient with chronic renal failure to excrete this drug without the development of prolonged neuromuscular blockade. Pancuronium has not been reported to produce problems in patients with renal failure.

SUMMARY

All general anesthetics employed clinically have significant and reversible effects on renal hemodynamics, water, and electrolyte excretion at concentrations in which they are usually employed for surgical anesthesia. Some of the mechanisms by which these effects are produced are discussed. The minimal depressant effect on renal function of epidural anesthesia is possibly related to local anesthetic effects on the central system and/or the kidney.

Methoxyflurane has been demonstrated to produce renal dysfunction when administered in high concentrations for prolonged periods of

time to obese patients. Metabolites of methoxyflurane including fluoride and/or oxalate appear to be the cause of this problem.

Problems of anesthetic management in patients with renal failure have been briefly summarized with specific attention to the undesirable effects of some neuromuscular blocking drugs.

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Effects of Anesthetics on Splanchnic Circulation and Metabolism

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In the last 10 years intense interest in "halothane hepatitis" plus simpler and more reliable technology for measuring splanchnic blood flow have led to a fuller understanding of the splanchnic effects of anesthetics. For the first time, a rational choice of anesthetic technique can be made for the patient with splanchnic organ dysfunction.

NORMAL PHYSIOLOGY OF SPLANCHNIC BLOOD FLOW

The splanchnic organs comprise all the abdominal contents except the genitourinary system; they include the liver, spleen, alimentary tract, pancreas, and gall bladder as well as the omentum. Since all splanchnic arterial blood drains eventually through the liver via the portal system, total splanchnic blood flow (SBF) is accurately reflected by total hepatic blood flow (HBF). For this reason, HBF and SBF are frequently used synonymously.

The liver is unique in receiving both well oxygenated blood from the hepatic artery and partly desaturated blood from the portal vein. These supplies encircle the hepatic lobule, mix together in the sinusoids, and drain via the central lobular vein and hepatic veins to the inferior vena cava. Mesenteric shunts and several portal-systemic connections allow additional splanchnic arteriovenous mixing.

Since the portal vein supplies roughly three quarters of total HBF, the liver depends largely on venous blood for its metabolic oxygen requirements. Fortunately, the splanchnic regions contributing to portal venous blood flow extract little oxygen in relation to their total arterial blood supply. Portal venous blood may, therefore, contain as much as 18 volumes per cent of oxygen and can significantly contribute to hepatic oxygenation, especially if hepatic arterial flow is compromised.[18] Even during a normal basal state, the liver satisfies about two-thirds of its 60 ml per min oxygen requirement from the portal vein.[19]

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Normally, SBF is 1.2 to 1.5 L per min. Both the total flow and its relative portal and arterial contributions vary with certain physiologic changes; however, in general, increased blood pressure raises blood flow, while increased vascular resistance diminishes flow. Although vessel diameter ultimately determines resistance in the arterial and venous circuits, control over vessel diameter differs in each.

Portal vein diameter is passively controlled. Intraluminal pressure from increased inflow or blood pressure causes venodilatation which further increases flow while perivascular edema or elevated intra-abdominal pressure results in venous compression and a decrease in flow. Thus, portal blood flow is particularly sensitive to changes in splanchnic blood volume. Some protection against splanchnic hypovolemia is afforded by a splenic reservoir containing fairly large amounts of high hematocrit blood with a high oxygen capacity. This reservoir can be discharged to maintain splanchnic blood volume during such stresses as hypoxia or hemorrhage.[8]

Hepatic artery flow, on the other hand, shows evidence of autoregulation and active control. Locally, "myogenic control" causes vascular smooth muscle contraction with vasoconstriction in response to increased transmural pressure. Central control is via nonmedullated sympathetic fibers from the celiac plexus and the superior and inferior mesenteric ganglia. While evidence exists for both alpha- and beta-sympathetic innervation to splanchnic organs and vessels, specific parasympathetic vasodilatory fibers are apparently absent.[14] Because arterial flow to the various splanchnic organs is in parallel, the proportion of total arterial flow to each organ is determined by the relative resistances of the vascular beds. The total flow to all organs is influenced as well by cardiac output and splanchnic oxygen requirements.

MEASUREMENT OF HEPATIC BLOOD FLOW

Over the years, HBF measurement techniques have ranged from crude estimates such as blood lost from severed hepatic vessels in a given time to sophisticated, noninvasive radiographic techniques utilizing calculated portal vein cross-sectional areas and the velocity of portal venous flow. More complete coverage of this topic can be found in the review by Bradley.[3]

All currently available techniques have significant limitations. Technically, several necessary assumptions regarding the liver's specificity for certain dyes, the absence of extrahepatic shunts, and the preservation of normal hepatic function during invasive monitoring are demonstrably unsound. Clinically, some uncertainty arises since measuring total hepatic flow does not differentiate that portion actually nourishing the hepatic cells.

Nearly all studies of anesthetic effects on splanchnic perfusion have estimated HBF by measuring hepatic clearance of intravascular indocyanine green. Following an intravenous priming bolus, dye is infused continuously at a rate adjusted to maintain a constant peripheral con-

centration. The liver is then assumed to be the only site of dye uptake and to retain dye in amounts equal to that being infused. Outflow dye concentration, obtained by sampling hepatic venous blood through an indwelling catheter, and inflow dye concentration, equal to peripheral concentration, then allow calculation of total HBF using the Fick principle:

$$\text{hepatic blood flow} = \frac{\text{mass of dye retained in the liver}^*}{\text{inflow concentration} - \text{outflow concentration}}$$

HEPATIC BLOOD FLOW RESPONSE TO SPECIFIC PHYSIOLOGIC ALTERATIONS

The effect on HBF of certain physiologic changes is reasonably well understood, and many of these changes are relevant during surgery and anesthesia.

Not infrequently, anesthetized patients receive vasoactive drugs. Alpha stimulators such as methoxamine increase systemic blood pressure but reduce HBF due to marked splanchnic arterial vasoconstriction. Norepinephrine does the same. Beta blockade with propranolol allows unopposed alpha activity indistinguishable from the effects of the former drugs.[14] If, however, ganglionic or alpha blockers (pentolinium or phentolamine) are administered concomitantly, propranolol's effect is blunted. Epinephrine, with mixed alpha and beta properties, produces uncertain effects. Although one study has demonstrated increased HBF, possibly due to increased cardiac output as well as vasodilation,[1] direct infusion of epinephrine into the splanchnic vasculature results in higher concentrations locally and vasoconstriction.[8]

Uncontrolled hemorrhage may precipitate a drastic fall in HBF. Although a 15 to 20 per cent acute blood loss in healthy volunteers produces no significant change in either splanchnic vascular resistance or flow, it does decrease splanchnic reservoir volume significantly.[17] Presumably, further bleeding would result in a systemic sympathetic response with splanchnic vasoconstriction. The combined effects of systemic hypotension and increased splanchnic vascular resistance could then seriously compromise the total HBF.

Not uncommonly, visceral traction during laparotomy produces systemic hypotension. A reflex arc presumably via sympathetic afferents results in efferent mediated dilatation of splanchnic capacitance vessels. As circulating blood pools in these vessels, venous return and cardiac output fall. The final result is systemic hypotension and proportionately diminished HBF.

Despite increasing use of controlled ventilation during anesthesia, hypoventilation with carbon dioxide retention may occur. Acute hypercapnea stimulates increased sympathetic activity and frequently raises

*See Appendix for derivation.

systemic blood pressure. A concomitant rise in splanchnic vascular resistance, though, results in decreased HBF. Following splanchnic denervation, hypercapnea produces splanchnic vasodilation instead and actually increases HBF.[4]

Respiration itself interferes periodically with splanchnic venous outflow and perhaps arterial inflow. During a spontaneous inspiration, the splanchnic contribution to inferior vena caval flow is sharply reduced while venous return from the kidneys and legs predominates. During passive exhalation, this pattern is reversed; splanchnic outflow becomes the major source of venous blood from the lower body.[13] Teleologically, this may provide a more even, steady blood supply to the right heart.

Anesthesia further accentuates this respiratory phenomenon. Increased splanchnic vascular resistance, decreased splanchnic blood volume, and fall in SBF are seen during intermittent positive pressure ventilation.[6] Mechanical interference with vascular transmural distending pressure may be solely responsible, or some as yet unknown reflex response to pulmonary inflation may exist.

Certain intrahepatic diseases grossly alter normal HBF. Hepatitis reduces HBF, probably secondary to hepatocyte swelling and increased parenchymal vascular resistance. For similar reasons, distention following gastrointestinal obstruction lowers HBF; peritoneal infection, though, increases SBF.[9] Cirrhosis of the liver may decrease HBF by half. Portasystemic shunting procedures, while often necessary to relieve life-threatening portal hypertension, do cause further deterioration of portal blood flow. Whether hepatic artery flow will then increase to maintain hepatic perfusion may become critical to hepatic function.[20]

ANESTHETIC EFFECTS ON SPLANCHNIC BLOOD FLOW

Many of the common anesthetic agents and techniques, including cyclopropane, methoxyflurane, halothane, and nitrous oxide, as well as spinal and epidural analgesia, have been studied for their effects on SBF. No published data are yet available for enflurane and isoflurane. Although most studies were conducted with male volunteers who had no operation, the picture of SBF variation during anesthesia is nevertheless now fairly complete.

Cyclopropane, in concentrations adequate for surgical anesthesia (16 to 21 per cent end expired concentration), roughly halves SBF. Increased sympathetic activity to the splanchnic viscera is thought to be the mechanism, since ganglionic blockade with hexamethonium lowers splanchnic vascular resistance and returns SBF to near normal despite lowering systemic blood pressure. The splanchnic vascular response to this sympathetic activity may also be enhanced since cyclopropane sensitizes the vessels to the actions of endogenous norepinephrine.[15]

Methoxyflurane reduces SBF to about half of control values. There appears to be no significant difference between light and deep anesthesia or controlled versus spontaneous ventilation. Although splanchnic

vascular resistance rises, as with cyclopropane anesthesia, abdominal angiography demonstrates a selective and specific constriction of the hepatic artery, suggesting a local mechanism rather than central stimulation. Some indirect evidence suggests that there is also portal venoconstriction in response to methoxyflurane. Since methoxyflurane also lowers systemic blood pressure, a further fall in HBF secondary to decreased perfusion pressure might be expected.[12]

Nitrous oxide apparently has no inherent effect on splanchnic vascular resistance or blood flow even when combined with thiopental, muscle relaxants, and controlled ventilation at "normal" volumes. If arterial carbon dioxide tension is allowed to increase, however, the expected splanchnic vasoconstriction occurs. Whether splanchnic blood flow itself changes is directly dependent on the systemic blood pressure.[7] As tidal volumes and minute ventilation are increased, splanchnic vascular resistance rises sharply and SBF drops to about half normal. Since adding exogenous carbon dioxide to the inspired gas mixture does not restore normal SBF, these changes may be due in large measure to combined diaphragmatic motion, increased intra-abdominal pressure, and peripheral blood pooling from elevated airway pressure. If, however, hypocapnea becomes marked (P_aCO_2 less than 18 torr), splanchnic vascular resistance diminishes somewhat toward normal allowing a slight increase in SBF.[5] This may reflect decreased sympathetic tone resulting from decreased P_aCO_2.

Halothane produces a marked decrease (about a third) in SBF but does not change splanchnic vascular resistance. Instead, systemic vasodilation and decreased cardiac output lower systemic and splanchnic perfusion pressure. Absence of the splanchnic vasoconstriction and systemic sympathetic discharge expected during hypotension implies that halothane in some way blunts the body's sympathetic responsiveness.[13] A paradoxical splanchnic vasodilatation observed during hypercapnea with halothane lends further support to this interpretation. This may represent a direct vascular action of carbon dioxide seen after blocking the normal sympathetic response to hypercapnea.

Like the general anesthetics, both spinal and lumbar epidural analgesia impairs HBF. High spinal anesthesia (T_5 sensory level) reduces HBF by a quarter to a third without significant change in splanchnic vascular resistance. The reduction in flow parallels the onset and duration of sensory and sympathetic blockade (about 90 minutes total) and varies directly with arterial blood pressure.[10]

HBF alteration during lumbar epidural analgesia depends on whether epinephrine is present in the local anesthetic. High epidural analgesia using lidocaine without epinephrine produces the expected 25 per cent fall in HBF. Interestingly, there is little change in the systemic blood pressure; instead, increased splanchnic vascular resistance accounts for the decreased hepatic perfusion. Previous studies have demonstrated increased cardiac output and systemic blood pressure with sufficiently high blood lidocaine levels, possibly due to central sympathetic stimulation.[2] Such stimulation, together with the slower onset of sympathetic blockade, may explain the unexpected difference between spinal and epidural analgesia without epinephrine.[11]

When epinephrine (1:200,000) is added to lidocaine, the anticipated systemic hypotension occurs but HBF does not initially fall. Here, the slower absorption of lidocaine still produces some increase in cardiac output, but there is also decreased splanchnic vascular resistance due apparently to the beta stimulating effects of absorbed epinephrine. After about 30 minutes, at which time the beta effects might be expected to disappear, cardiac output and splanchnic vascular resistance return to near control values, and the characteristic 25 per cent decrease in HBF is observed.[11]

METABOLIC EFFECTS OF ALTERED SPLANCHNIC BLOOD FLOW

A knowledge of SBF alone provides only indirect information about changes in liver metabolism. The large number of liver function tests available bears testimony to the difficulty of adequately assessing the overall function of so complex an organ. One general indication of organ well-being, however, is the absence of hypoxic metabolism.

During aerobic metabolism, which provides the maximum yield of high energy phosphate (ATP), glucose is first converted to pyruvic acid in the cell cytoplasm. Normally the pyruvic acid is then oxidized via acetyl Co A to CO_2 in the mitochondria (see article by Levitt in this symposium). If, however, there is limited metabolic oxygen available, an alternative pathway of anaerobic glycolysis exists in which pyruvic acid is converted to lactic acid still yielding limited ATP. This lactic acid accumulates for later reconversion to pyruvic acid and further oxidation when more oxygen is available. Thus an increasing blood lactate/pyruvate (L/P) ratio can be used as an indicator of ongoing cellular hypoxia.

Three anesthetics have so far been studied for their effects on hepatic oxygenation.[12, 16] Of these, halothane and methoxyflurane do not significantly alter the hepatic venous L/P ratio. Cyclopropane, however, does result in a significant elevation of the L/P ratio and the production of "excess" lactate.* These alterations persist when SBF is increased by administration of a ganglionic blocking agent. Beta adrenergic blockade, although it further lowers SBF, abolishes "excess" lactate accumulation. This finding suggests that lactate production in this case represents a metabolic consequence of increased sympathetic activity, not true organ hypoxia. Present evidence suggests that, in healthy volunteers, clinically observed changes in SBF do not cause splanchnic organ hypoxia.

Since not all patients have healthy splanchnic organs, a more critical ranking of anesthetics may help differentiate among their splanch-

*The splanchnic arteriovenous "excess" lactate (A−V XL) is defined as:

$$A-V\ XL = (L_V - L_A) - (P_V - P_A)\frac{L_A}{P_A}$$

where L_A and L_V are the hepatic arterial and venous lactate concentrations and P_A and P_V are arterial and venous pyruvate concentrations (units in millimoles per liter).

nic effects. Typically, reduced SBF is accompanied by some reduction in oxygen consumption. Since these reductions are not necessarily equal for all anesthetics, it is possible to construct a table[12] comparing their ratios. A ratio of 1.0 indicates equal reduction of both SBF and splanchnic oxygen consumption, while lower ratios indicate residual oxygen consumption in excess of remaining perfusion, a less desirable situation. Current rankings of anesthetics are:

Halothane	0.82
N_2O-curare-normocarbia*	0.82
Cyclopropane	0.79
Spinal	0.73
N_2O-curare-hypocarbia*	0.59
Methoxyflurane	0.55

Clearly, methoxyflurane and nitrous oxide with hypocarbia show disproportionately great reductions in SBF.

CLINICAL APPLICATIONS

Anesthesia, in general, reduces SBF and thus splanchnic oxygen delivery from one-quarter to one-half of normal. However, there is no clear evidence that any anesthetic causes harm in healthy persons. The possible relationship of SBF alterations to postoperative hepatic necrosis ("halothane hepatitis") has also been proved untenable. In the patient with marginal splanchnic circulatory adequacy, though, those anesthetics with low SBF/O_2 ratios must be suspect. Conditions associated with reduced availability of oxygen to the liver include intrahepatic disease (cirrhosis, hepatitis, exposure to hepatotoxic substances) as well as portal vein or hepatic artery obstruction. Hypermetabolic states, systemic hypoxia, and systemic circulatory inadequacy (shock, hemorrhage, or hypotension) may also impair oxygen delivery to the liver. It is in patients such as these that anesthetic techniques with high ratios of splanchnic flow to oxygen consumption may be preferable.

Appendix. *Derivation of Equation for Calculation of Hepatic Blood Flow*

1. In general, dye mass = concentration × flow ($M = C\dot{Q}$).
2. By the conservation of mass, mass of dye entering liver = mass retained in liver + mass leaving liver ($\dot{Q}_A C_A = MR + \dot{Q}_V C_V$).
   where $\dot{Q}_A$ = arterial inflow rate, C_A = arterial concentration,
   $\dot{Q}_V$ = venous outflow rate, and C_V = venous concentration.
3. Since arterial inflow = venous outflow ($\dot{Q}_A = \dot{Q}_V$), then equation (2) can be rearranged to read $\dot{Q} = \frac{MR}{C_A - C_V}$.

*Patients hyperventilated—exogenous carbon dioxide added for normocarbia.

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Anesthesia and the Immune System

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The function of man's immune system is to recognize and respond to potentially harmful foreign substances including bacteria, viruses, tumor cells, and foreign tissue. In the perioperative period, this system should play a key role in the prevention of infection and of tumor seeding during cancer surgery. Anesthesia and operation, however, may impair the immune system so that bacterial growth and tumor spread may occur more readily, and host response to transplanted tissue and allergenic substances may be altered. It is the purpose of this article to outline briefly some basic immunologic concepts. The effects of anesthesia and operation on immune function will be outlined and suggestions will be presented regarding the anesthetic management of patients at risk from infection or tumor spread.

The Immune Process

Cells of lymphoid origin mediate the immune response by recognizing and reacting to foreign molecules. Initially, polymorphonuclear neutrophils (PMN's) and monocytes migrate toward a foreign substance in response to locally increased blood flow and to chemotactic factors. These are generated by antibody-antigen-complement interaction or other less specific serum factors including elements of the properdin system and products of Hagemann factor activation. The next step is phagocytosis, an energy dependent process of antigen engulfment which may be aided by the coating of the antigen with serum proteins (opsonization—preparation for eating). These opsonins may be either specific immune antibodies, natural antibodies, or components of the complement or properdin systems which act less specifically to coat foreign substances. Following phagocytosis, intracellular processes involving lysozymes and the production of hydrogen peroxide ultimately lead to antigen destruction. Finally, through the interaction of both thymic and bone marrow derived lymphocytic cells, the antigen is prepared for programming into immunologic memory, so that future exposure to the antigen will result in proliferation of lymphocytes and rapid antibody production from sensitized plasma cells. It is important to note that the above processes are to a great extent interrelated, are energy dependent,

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both aerobic and anaerobic, and can be influenced by a number of factors including corticosteroids, cylic AMP levels, catecholamines, a variety of drugs,[3, 13, 14, 25, 26] and the presence of disease (infection, cancer, trauma, or congenital lack of specific components).[18, 19, 23] Periodic variation in immune function has been described in normal man.[2]

The net function of the immune system, then, is the localization, recognition, and destruction of potentially harmful antigens with subsequent appropriate programming of these molecules into immunologic memory. For more complete discussion of the immune system several excellent references are available.[1, 6, 7, 15, 20, 24]

Immunologic Effects of Anesthesia and Operation

Studies both in vivo and in vitro have shown that anesthesia can interfere with many phases of the immune response.[5] As early as 1911, Graham[17] demonstrated that ether anesthesia inhibited leukocyte phagocytic activity. Bruce has shown that phagoycte mobilization was decreased by halothane in mice.[4] That lymphocyte function can be compromised by a variety of anesthetic agents in vivo is shown by decreased antibody production, impairment of complement fixation, and inhibition of lymphocyte transformation.[2, 6, 22] Lymphocyte transformation is a sequence of RNA, DNA, and protein synthesis with subsequent cell division occuring when resting lymphocytes are stimulated by specific antigen or nonspecific mitogen such as phytohemagglutinin (PHA). Lymphocyte transformation may be depressed following in vitro exposure to halothane as well.[12] The activity of already formed antibodies does not appear to be compromised by anesthesia.

PMN intracellular killing mechanisms as assayed by NBT reduction have also been shown to be depressed following anesthetic exposure in vivo but not in vitro.[8, 11, 22] This is a test in which PMN's are incubated with nitroblue tetrazolium (NBT) dye and the amount of dye reduced to formazan is determined spectrophometrically or cytologically.

While clinical concentrations of anesthetics have been shown to interfere reversibly with both aerobic and anaerobic metabolism, this does not appear to be the mechanism for postoperative immunologic depression. If it were, one would expect that immune suppression would be seen only in the presence of the anesthetic; in fact, postoperative immunologic compromise may persist for several days (Lecky, J. H.: Unpublished data).

The "stress" response to surgery involves initial catecholamine release with subsequent elevation of corticosteroid levels. In a study of the effects of nitrous oxide-d-tubocurarine (N_2O,O_2,dTc) anesthesia on white cell function in human volunteers undergoing cerebral blood flow studies (essentially anesthesia without surgery), depression in NBT reduction and lymphocyte reactivity was associated with cortisol elevation, increases in neutrophil count, and slight reductions in lymphocyte count.[22] These changes in white cell function were all compatible with steroid effect. N_2O and dTc have no in vitro effect on these tests. Cullen recently studied the relationship of immune depression (as assayed by lymphocyte reactivity) with surgical trauma.[9] Operations were graded

on a trauma scale which ranged from anesthesia without surgery to massive surgical trauma with minimal anesthesia. Steroid levels were not obtained but the degree of immune depression closely paralleled the extent of surgical trauma. In a study of patients undergoing staging laparotomy (splenectomy, liver biopsy, and multiple abdominal node biopsy) for Hodgkin's disease, it was observed that a "deep anesthetic technique" (halothane-relaxant) resulted in less immune depression than did a "light technique" (N_2O,O_2,dTc) (see reference in preceding paragraph). As measured by lymphocyte transformation and NBT reduction, white cell function was depressed to 50 per cent of control on the first postoperative day following a halothane anesthetic and to 30 per cent following N_2O,O_2,dTc anesthesia with return to control values on days 4 and 7, respectively. The fact that deeper anesthetic techniques and minimal degrees of surgical trauma result in less immune compromise than lighter anesthetic techniques and/or major surgical trauma is attributable to the degree of catecholamine and corticosteroid release, i.e., the stress response associated with major surgical trauma.

The clinical significance of in vitro test results is often difficult to interpret; however, many disease states associated with high incidences of infection[19] manifest depressed in vitro immunologic test results. For the average patient undergoing operation, a 20 per cent reduction in immune function probably poses no great problem. However, it is in the patient with compromised immune function or in the critically ill patient where prolonged operation may be necessary and where a light anesthetic technique is likely to be used that the consequences of immune compromise are least desirable and yet are the most apt to be seen.

Management of the High Risk Patient

Given the fact that anesthesia and operation impair immune functions, what steps might one take to minimize the immune compromise? Preoperatively, care should be taken to insure optimal nutritional status and to treat any active infection. The fact that the immune system is depressed postoperatively also adds to our conviction that patients with a cold or active infections should not be operated upon unless surgery cannot be delayed. Prophylactic antibiotics might be considered. Intraoperatively, surgical technique should be impeccable, rapid, and atraumatic.[16] Care should be taken to insure adequate circulatory blood volume so that perfusion of white cells to potential areas of infection can be maintained.

Theoretically, it would appear that in order to minimize the "stress" response, a depth of anesthesia as great as possible compatible with cardiovascular tolerance theoretically be employed, and agents which release catecholamines (N_2O, fluroxene, cyclopropane) should be avoided. Unfortunately, because of shock, hypovolemia, or a failing myocardium, one is often unable to administer more than neuromuscular blockade and mild analgesia to the critically ill patient.

Regional or local anesthetic techniques are not necessarily a good choice on immunologic grounds. While less immune depression is seen

during abdominal surgery under spinal anesthesia, the ultimate postoperative immunologic depression is comparable to that seen with general anesthesia (see Lecky, above). Local anesthetics in clinical concentrations have been shown to directly inhibit white cell function in vitro.[10] While local anesthetics do not appear to have systemic immune effects, they are capable of inhibiting white cell function in the area into which they have been injected.

At present, then, we are limited in our ability to optimize immune function in the surgical patient. Surgical trauma results in immunosuppression. Much work remains in determining the anesthetic agent or technique which will provide the least immunologic compromise. The possibility for a pharmacologic approach to *enhancement* of white cell function is an intriguing one and may, in fact, be a most fruitful area for future investigation.

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The Biochemical Basis of Anesthetic Toxicity

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This article considers three aspects of the cellular metabolism of inhalational anesthetics: first, what anesthetics do to cells—specifically, the effects of anesthetics on mitochondrial metabolism and its implications; second, what cells do to anesthetics—the biotransformation of the inhalational anesthetics; and finally, the relationship of biotransformation to organ toxicity. Additional information on these topics can be found in recent reviews.[18, 24]

REVIEW OF CELLULAR METABOLISM

Inhalational anesthetics have been shown to affect cellular carbohydrate and energy metabolism. In order to see these effects in perspective, it is necessary first to review some aspects of normal cellular metabolism.

Within cells, the hydrolysis of the terminal phosphate bond of adenosine triphosphate (ATP) provides the energy for such processes as muscular contraction, anabolic reactions (including neurotransmitter synthesis), and the running of ion pumps (to maintain ion gradients and membrane potentials). The products of this hydrolysis are adenosine diphosphate (ADP) and inorganic phosphate (P_i).

$$ATP \longrightarrow ADP + P_i + \text{Free Energy}$$

ATP is formed through the opposite process: an energy-yielding chemical reaction is coupled to the combining of ADP and P_i to make ATP. The energy of the reaction is thereby stored in the terminal phosphate bond of ATP, which is called a high-energy phosphate bond and is designated ~ P.

Energy in the form of ~ P can be stored in several other compounds, from which the ~ P can be transferred to ADP. An example is creatine phosphate (Cr ~ P), whose reaction with ADP is catalyzed by the enzyme creatine phosphokinase.

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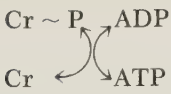
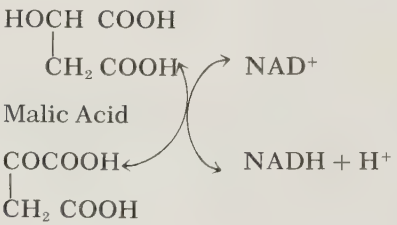


Creatine phosphate is an important source of high energy phosphate in muscle.

ATP is formed in the course of both the anaerobic and aerobic breakdown of glucose. The anaerobic pathway, called glycolysis (Embden-Meyerhof pathway) results in the formation of 2 moles of lactic acid, 2 moles of water, and 2 moles of ATP per mole of glucose. The enzymes which catalyze this process are located in the cytosol.

The aerobic pathway yields 6 moles of CO_2, 6 moles of water, and 38 moles of ATP per mole of glucose. It consists of the Krebs cycle (also called the citric acid or tricarboxylic acid cycle) and the electron transport chain. When this pathway is functioning, pyruvate is not reduced to lactate, as in glycolysis, but instead pyruvate enters the citric acid cycle where it undergoes successive steps of oxidation (oxidation = loss of electrons). The electrons lost by the carbohydrate substrate are taken up by another compound, which is thereby reduced. Those compounds which accept electrons in this cycle include nicotinamide adenine dinucleotide (NAD^+, formerly called DPN), flavoprotein (F_p), and nicotinamide adenine dinucleotide phosphate ($NADP^+$). An example of the coupling of substrate oxidation to NAD^+ reduction is the oxidation of malic acid to oxaloacetic acid by malic dehydrogenase.



Oxaloacetic Acid

The NADH or reduced F_p formed during the oxidation of Krebs cycle intermediates is in turn oxidized by losing electrons to components of the electron transport chain (Fig. 1). Through a succession of coupled oxidation-reduction reactions, the electrons are transported by the cytochromes to molecular oxygen, which is reduced ultimately to water. Each step in the electron transport chain is an energy-yielding reaction. At three sites along the cytochrome chain, energy is stored by coupling electron transport to the phosphorylation of ADP to form ATP. This is called "oxidative phosphorylation." Drugs which separate electron transport from oxidative phosphorylation are called "uncoupling agents." Theoretically, mitochondria respiring NADH-linked substrates should phosphorylate three molecules of ADP for each atom of oxygen utilized. Uncoupling agents cause a decrease in this P/O ratio.

The enzymes which comprise the citric acid cycle and the electron transport chain are bound by membranes in subcellular organelles called mitochondria. Relatively pure suspensions of mitochondria have been prepared from brain, liver, and other tissues, and their properties have been studied in vitro. Anesthetics cause alterations in the function of the isolated mitochondria. Among the methods used to study these effects are the following.

1. Polarographic techniques (oxygen electrodes) facilitate the measurement of oxygen consumption in the presence of drugs.
2. Spectrophotometric techniques help to identify the site of action of inhibitors by identifying which components of the respiratory chain become more oxidized and which become more reduced in the presence of inhibitors.
3. Calcium fluxes are measured using the dye murexide and radioactive calcium.
4. Electron microscopy is used to demonstrate changes in the conformation of mitochondrial membranes under various conditions.

EFFECTS OF BARBITURATES ON MITOCHONDRAL FUNCTION

The effects of barbiturates and inhalational anesthetics on mitochondrial function have been reviewed critically by P. J. Cohen.[13] Both thio- and oxybarbiturates reduce the oxygen uptake of liver and brain mitochondria which are utilizing NADH-linked substrates. Spectrophotometric techniques have localized the site of this action at the level of NADH dehydrogenase. That is, barbiturates inhibit the transfer of electrons from NADH to flavoprotein (see Fig. 1). Oxybarbiturates (e.g., amobarbital) cause no uncoupling of oxidative phosphorylation, but thiobarbiturates (e.g., thiopental) reduce the P/O ratio of rat liver mitochondria, in addition to inhibiting respiration. However, the concentrations of barbiturates necessary to demonstrate these effects may be ten times the clinical blood concentrations. It is generally believed that mitochondrial effects are not involved in the action of usual doses of barbiturates.

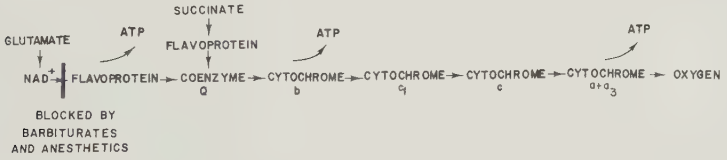


Figure 1. The mitochondrial electron transport chain, demonstrating the sites of glutamate and succinate oxidation and the three sites of oxidative phosphorylation. Each component of the chain is reduced by accepting electrons from the preceding component and oxidized by passing electrons to the next component. Oxygen is the final electron acceptor. High doses of barbiturates and anesthetics inhibit the NADH-linked pathway, but do not inhibit succinate oxidation.

EFFECTS OF INHALATIONAL ANESTHETICS ON MITOCHONDRIAL FUNCTION

In a continuing series of studies,[13-15, 45] Cohen and his co-workers have equilibrated rat liver mitochondria with clinically relevant partial pressures of inhalational anesthetics. They have measured the oxygen uptake of the mitochondria as a function of anesthetic concentration in the presence of various substrates. Figure 2 illustrates an experiment in which rat liver mitochondria were exposed to halothane (Fluothane) while utilizing glutamate, an NADH-linked substrate. When substrate, oxygen, and ADP were present (mitochondrial State 3), halothane caused a dose-related decrease in oxygen uptake. This effect was reversible when the halothane concentration was less than 2 per cent. When ADP was omitted from the reaction medium (mitochondrial State 4), halothane did not inhibit the already low oxygen uptake. Since State 3 respiration is limited only by the capacity of the respiratory chain and State 4 respiration is limited by the availability of ADP, it appeared that halothane was acting on a component of the respiratory chain. When the experiment was repeated with succinate, a substrate not linked to the cytochromes through NADH, halothane did not inhibit State 3 respiration. Therefore, the site of halothane action is at the level of NADH dehydrogenase. High concentrations of halothane can disrupt permanently the mitochondrial membrane, and cause uncoupling of oxidative

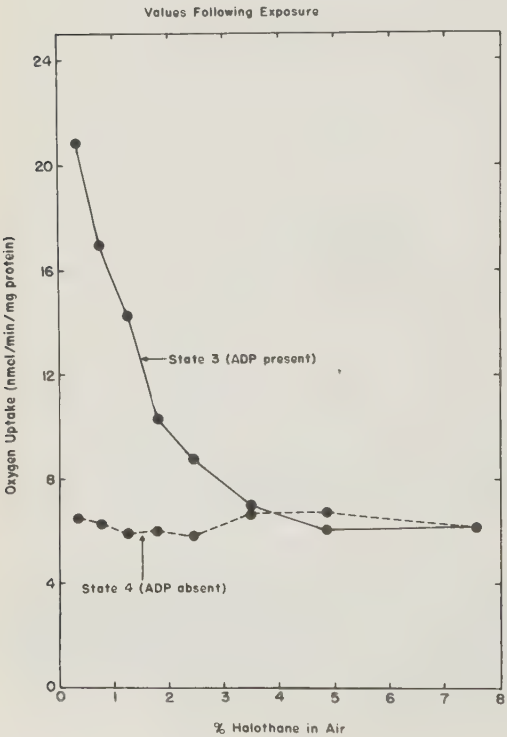


Figure 2. Effect of halothane on oxygen uptake of rat liver mitochondria utilizing glutamate as substrate. Mitochondria were equilibrated at 0°C with halothane in air. Oxygen uptake was measured at 25°C. State 3 respiration is inhibited in a dose-related manner by halothane. (Modified from Cohen, P. J., and Marshall, B. E.: Effects of halothane on respiratory control and oxygen consumption of rat liver mitochondria. *In* Fink, B. R. (ed.): Toxicity of Anesthetics. Baltimore, Williams and Wilkins Co., 1968, pp. 24–36. Used with permission.)

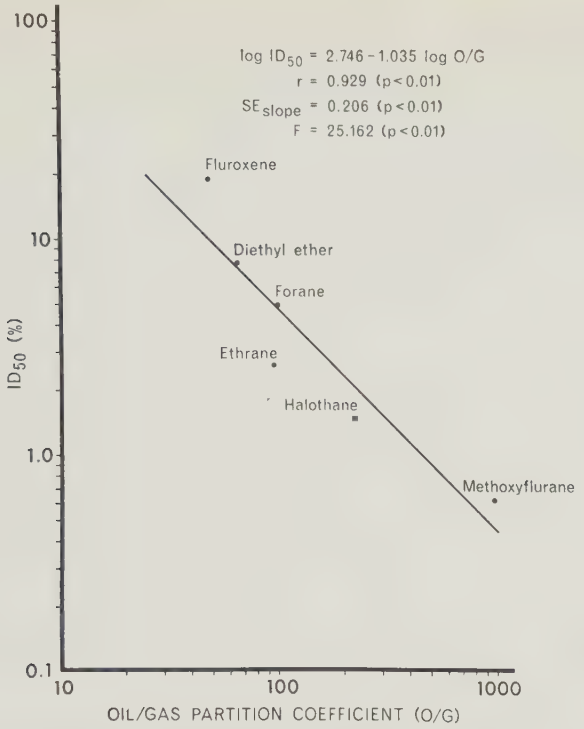


Figure 3. Correlation between the potency of anesthetics in inhibiting mitochondrial State 3 glutamate oxidation (ID_{50}) and their lipid solubilities (O/G). The correlation coefficient is 0.93, demonstrating a good correlation. (Reproduced from Nahrwold, M. L., and Cohen, P. J.: The effects of Forane and fluroxene on mitochondrial respiration: Correlation with lipid solubility and in-vivo potency. Anesthesiology, *38*:437–444, 1973. Used with permission.)

phosphorylation. However, anesthetics are unlikely to be uncoupling agents at clinical concentrations.[42]

Effects on State 3 respiration similar to those of halothane have been found for diethyl ether, methoxyflurane (Penthrane), enflurane (Ethrane), fluroxene (Fluomar), and isoflurane (Forane). Nahrwold and Cohen[45] have attempted to relate the mitochondrial effects of anesthetics with their lipid solubilities and in vivo potency. Using data for the six anesthetics mentioned above, they constructed a graph of the concentration of anesthetic required to inhibit State 3 glutamate oxidation by 50 per cent (ID_{50}) versus the oil/gas partition coefficient (O/G) of each anesthetic (Fig. 3). The correlation coefficient of the line they obtained was 0.93. The same correlation coefficient was obtained when ID_{50} was plotted against an in vivo measure of anesthetic potency. This was not a surprising finding, since the correlation between O/G and in vivo potency was known to be 0.998. However, it suggested to these investigators that inhibition of mitochondrial State 3 respiration might be used to predict in vivo anesthetic potency.[44] They tested the in vivo and in vitro activity of several aliphatic hydrocarbons and fluorocarbons and found that compounds which lacked central nervous system effects in mice did, indeed, fail to inhibit State 3 glutamate oxidation in mitochondria.

However, compounds which caused *convulsions* in mice had the same effect as *anesthetics* on mitochondrial respiration. Furthermore, two compounds which exhibited antagonistic properties in vivo were additive when tested in mitochondria. The in vitro system, therefore, cannot be used to predict anesthetic activity in vivo.

Miller has measured the oxygen uptake of synaptosomes, or nerve-ending particles, exposed to halothane.[43] This preparation, which consists of the pinched-off terminal portions of brain axons, responded to halothane with a decrease in respiration similar to that of mitochondria. This is significant because synaptosomes contain within their limiting membranes not only mitochondria, but also the glycolytic enzymes and the machinery for neurotransmitter synthesis and release. They resemble intact neurons rather than subcellular organelles, and have been productive tools in neurochemical research.[59]

Mitochondria may have an important role in the regulation of intracellular calcium. When actively respiring or when exogenous ATP is provided, these particles take up calcium from their suspending medium. Rosenberg and Haugaard[50] have shown that halothane, in concentrations similar to those seen in the brain during anesthesia, can inhibit calcium uptake by rat brain mitochondria. If this effect is great enough to raise the cytoplasmic calcium concentration at nerve terminals, it could have marked effects on nerve cell excitability and neurotransmitter release. These observations have been confirmed, in part, by Miller[43] and have been incorporated into a biochemical theory of anesthesia.[32]

RELATIONSHIP OF MITOCHONDRIAL EFFECTS TO CLINICAL ANESTHESIA

Clinical anesthesia with most anesthetics is associated with a decrease in the cerebral metabolic rate for oxygen.[51] Since anesthetics also decrease the mitochondrial respiratory rate, the question arises as to whether the inhibition of mitochondrial respiration is the explanation for the decreased cerebral oxygen uptake, and whether, in fact, the mitochondrial effects are the biochemical basis of the anesthetic state. If one assumes that the brain is the major site of anesthetic activity, one approach to answering both of these questions is to examine the amounts of ATP and glucose in the brain and the rate of glucose utilization and lactate production during anesthesia. Since inhalational anesthetics inhibit the aerobic pathway for the formation of high-energy phosphate bonds during anesthesia, the rate of formation of ATP by glycolysis would have to increase markedly if the energy requirements of the brain remained constant. The brain would react metabolically as though it were anoxic, because electrons could not be transferred to oxygen from NADH and citric acid cycle intermediates. Glucose utilization and lactate production would increase, and there might be a fall in the level of tissue ATP if enough could not be formed by glycolysis. However, this is not what happens. Brunner and Passonneau[5] found that light halothane and ether anesthesia in mice caused no change in

the brain ATP level, an increase in brain glucose level, and a decrease in brain lactate. They found also that anesthesia was associated with a decrease in the rate of utilization of ATP, creatine phosphate, and glucose. Other recent studies also have reported results consistent with the concept that inhalational anesthetics[41, 60] and barbiturates[19] reduce the energy expenditure of the brain as much as or more than they reduce energy production. Therefore, the reduced oxygen uptake of the brain during anesthesia probably reflects a decreased demand for ATP. Since the amount of ATP in the brain is not reduced during anesthesia, it is unlikely that inhibition of mitochondrial oxidative phosphorylation is the biochemical basis of anesthesia.

One might ask whether the studies of mitochondria bear any relevance to clinical anesthesia. With respect to the effect of anesthetics on the energy-storing function of mitochondria, there is no evidence that it is important in the brain during clinical anesthesia. More information is needed before the question can be answered with respect to myocardial depression by anesthetics.[40, 48] The interference by anesthetics with mitochondrial calcium uptake may have profound signifance, but at present this is speculative since there is no information about the effect of anesthetics on intracellular calcium levels.

BIOTRANSFORMATION OF INHALATIONAL ANESTHETICS

Until the mid-1960's it was thought that the inhalational anesthetics, with the exception of trichloroethylene (Triline),[1] were eliminated unchanged through the lungs as they were absorbed. It was generally believed that the action of these agents was dependent on their physical properties, and that they were not involved in any chemical transformations within the body. There is still general agreement on the first part of this belief. Although compounds with sedative properties are formed during the biotransformation of some anesthetics (e.g., bromide from halothane and ethanol from diethyl ether), there is no evidence that the action of any inhalational anesthetic arises from its metabolites. Almost all of the major inhalational anesthetics undergo biotransformation of some degree, which for methoxyflurane may be about 50 per cent of an inhaled dose. With respect to chloroform, fluroxene, methoxyflurane, enflurane, and possibly halothane, the organ toxicity of these agents is due to one of the anesthetic's degradation products. With these compounds, it is clear that the term "biotransformation" is not synonymous with "detoxification." As a rule, biotransformation results in compounds which are less lipid-soluble and more polar and, therefore, more easily excreted in the urine. However, the final metabolite or an intermediary metabolite may be a compound with high chemical reactivity or toxicity.

An inhaled anesthetic may be handled by the body in one of three ways:[54] (1) it may be eliminated unchanged, principally through the lungs; (2) it may be metabolized by enzyme systems, principally in the liver (the products would be eliminated mostly in the urine; volatile products like CO_2 would be eliminated by the lungs); and (3) it may un-

dergo spontaneous (nonenzymatic) breakdown and be eliminated by one of the above routes.

The methods used to study the metabolism of inhalational anesthetics include a large variety of chemical and tracer techniques. The most direct chemical technique involves administering a known dose of anesthetic, collecting the exhaled gas over a period of time, and analyzing it (usually by gas chromatography) for anesthetic content. It is then possible to calculate the fraction of the dose that was not eliminated through the lungs, presumably having been transformed to a nonvolatile metabolite, although such studies should also consider the amount of anesthetic which diffuses through the skin. Another chemical approach is to analyze the urine and feces for metabolites. This is most feasible when the compound being analyzed is normally present only in very small amounts. Fluoride, bromide, and the halogenated organic acids are examples of such compounds. Halsey, Sawyer, et al.[25] have used the difference in anesthetic concentration in the arterial and hepatic venous blood under equilibrium conditions to calculate the amount of anesthetic removed from the blood by the liver and presumably metabolized.

Most tracer studies have used the radioactive label ^{14}C. In an early study, $^{14}CO_2$ was detected after the administration of ^{14}C-cyclopropane, but the metabolism could not be quantitated.[55] Another approach was that of Cohen and Hood[12] who performed low-temperature autoradiography on hemisections of mice that had been given ^{14}C-halothane. By comparing autoradiographs performed before and after the sections were heated to remove unchanged halothane, they were able to demonstrate the presence of nonvolatile metabolites of halothane in the liver and other organs. However, this technique does not identify the nonvolatile compounds. As an extension of this general approach, Van Dyke and Wood[56] prepared subcellular fractions from rat livers that had been perfused with blood containing ^{14}C-halothane, and showed that the radioactivity was predominantly in the microsomal fraction (see below). Many studies have combined the use of radioactive tracers with chromatography and other analytic techniques in order to obtain both quantitative and qualitative information on biotransformation.

THE MIXED-FUNCTION OXIDASE SYSTEM

The site of biotransformation of the inhalational anesthetics and other compounds foreign to the body is the endoplasmic reticulum, principally that of the liver. The endoplasmic reticulum, which includes the mixed-function oxidase enzyme system, can be separated from other cellular structures by homogenizing the liver and subjecting the homogenate to differential centrifugation. In this process the membranes of the endoplasmic reticulum form into small spheres, called microsomes, that sediment between 30,000 and 100,000 g. Recent work with this in vitro preparation has demonstrated that it is capable of releasing inorganic fluoride from methoxyflurane,[57] and that halothane, methoxyflurane, and enflurane bind to one of its components (cytochrome P-450) in a manner identical to that of hexobarbital, one of its classical

substrates.[53] Brown has reviewed those aspects of the hepatic microsomal enzyme system and its induction that are relevant to volatile anesthetics.[3] His review should be consulted for additional information and references.

The initial reaction in the biotransformation of the volatile anesthetics and many other drugs is an oxidation involving the microsomal mixed-function oxidase system. The heart of this system is the enzyme cytochrome P-450 (so called because of its strong absorption peak under certain conditions at 450 nm). Cytochrome P-450 is characterized by the capacity to react with a wide variety of substances foreign to the body. The proposed electron-transfer scheme for cytochrome P-450 is shown in Figure 4. A drug combines with the oxidized form of cytochrome P-450. This complex is reduced by electrons which come ultimately from reduced NADPH. The reduced cytochrome P-450 and the drug are then both oxidized by molecular oxygen. The transfer of electrons from NADPH to oxidized cytochrome P-450 proceeds via a flavoprotein, cytochrome P-450 reductase, which is capable also of reducing cytochrome C. The oxidized drug may undergo further degradation, and the products may be conjugated, as to glucuronic acid.

Many drugs are capable of increasing the activity of the hepatic microsomal enzyme system. Administration of phenobarbital, for example, for a few days results in an increase in endoplasmic reticulum within hepatic cells and an increase in the amount of microsomal protein that can be isolated. (For references see Brown.[3]) This process, microsomal enzyme induction, modifies the toxicities of chloroform, methoxyflurane, and fluroxene through increased metabolism of the anesthetic and increased production of a toxic metabolite.

A recent paper by Brown and his colleagues[4] illustrates several points in the relationship of drug metabolism to toxicity. Previous investigations had shown that hepatic necrosis in rats following chloroform anesthesia could be enhanced by pretreatment of the animal with phenobarbital and decreased by treatment with the enzyme-inhibitor disulfiram (Antabuse).[10] In addition, hepatotoxicity had not been seen in newborn animals, presumably because their microsomal enzyme systems were not fully functional. Thus, it appeared that toxicity was

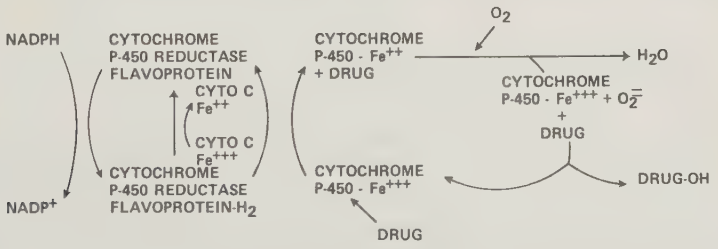


Figure 4. Proposed electron-transfer system of the hepatic mixed-function oxidase system. Drugs combine with the oxidized form of cytochrome P-450. After cytochrome P-450 is reduced, oxygen combines with the complex, oxidizing both cytochrome P-450 and the drug. Cytochrome P-450 may be reduced by electrons transferred from NADPH via cytochrome P-450 reductase, as shown, or possibly from NADH by a pathway not shown. (Modified from Brown, B. R., Jr.: Hepatic microsomal enzyme induction. Anesthesiology, 39:178–187, 1973. Used with permission.)

linked to the ability to metabolize chloroform. In Brown's study chloroform anesthesia was followed by hepatic necrosis in rats pretreated to induce microsomal enzymes. Hepatic necrosis was preceded by a marked fall in hepatic reduced glutathione (GSH, a sulfhydryl tripeptide that acts as an antioxidant). This was significant because other work had suggested that free radical intermediates of chloroform metabolism might react with, oxidize, and disrupt hepatic lipids in the pathogenesis of hepatic necrosis. GSH has the ability to "quench" the free radicals and thereby protect the cellular lipids. In addition, rats given a drug (diethyl maleate) which depleted hepatic GSH developed hepatotoxicity following chloroform anesthesia in the absence of enzyme induction.

This study demonstrates that the hepatotoxicity of chloroform anesthesia is not simply a direct toxic effect of the chloroform molecule on the hepatocyte. For hepatotoxicity to occur the rate of formation of free radicals must exceed the capacity of the hepatic GSH to "quench" them. This could arise from induced microsomal enzyme activity (starvation or drug pretreatment), or from a drug-induced reduction in GSH. The toxicity results from the *interaction* of chloroform with a susceptible liver.

It is unlikely that a study like this will be done in humans, but there are suggestions that enzyme induction plays a role in human anesthetic toxicity. The enzymes of hepatic microsomal electron transfer are present in humans, but their activity may vary considerably from one individual to another.[3] The well-known interaction between dicumarol metabolism and barbiturate administration[21] is one piece of evidence suggesting that hepatic microsomal enzymes are inducible in man by the same agents that induce in the rat. A case has been reported of fatal massive hepatic necrosis following fluroxene anesthesia in an epileptic patient who was taking large doses of phenobarbital and diphenylhydantoin (Dilantin),[47] two known enzyme-inducing drugs. The necrosis was evident within hours after an uneventful 6-hour anesthetic. The clinical course and pathologic findings were not typical of viral hepatitis. It is possible that enzyme induction in this case altered the rate or the pathway of fluroxene metabolism and led to the accumulation of toxic metabolites. More recently, this possibility has been confirmed in rats[26] (see below).

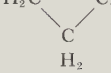
BIODEGRADATION AND ORGAN TOXICITY OF INHALATIONAL ANESTHETICS

This section provides information about the major metabolic products, of the inhalational anesthetics and some aspects of their organ toxicities. No attempt is made to present details of the metabolic pathways. The information is summarized in Table 1.

Nitrous Oxide

Nitrous oxide is the only inorganic inhalational anesthetic in common use. There has been no direct demonstration of its biotransforma-

Table 1. *Biotransformation of the Inhalational Anesthetics*

ANESTHETIC	TRADE NAME	FORMULA	PER CENT METABOLIZED	PRINCIPAL METABOLITES	NOTES	REFS.
Nitrous oxide		N_2O	0 per cent (?)		Metabolism may be demonstrated when isotopes are available.	10
Cyclopropane			?	CO_2, small amount	Quantitation has been technically difficult.	55
Diethyl ether		$H_3C—CH_2—O—CH_2—CH_3$	4 per cent (mice)	CO_2, acetate (acetaldehyde) (ethanol)	Breakdown products are normal body compounds.	20,54
Chloroform		$HCCl_3$	>4 per cent (mice)	CO_2 + (?)	Toxicity is result of its metabolism.	4,10
Trichloroethylene	Trilene	$Cl—CH=CCl_2$	20 per cent (man)	10 per cent trichloracetic acid 10 per cent trichloroethanol	Metabolites accumulate with repeated exposure.	22
Halothane	Fluothane	$F_3C—CBrClH$	11 to 25 per cent (man)	$F_3C—COOH$ Br^-, Cl^-	Trifluoroacetic acid appears as trifluoroacetylethanolamine. May be antigenic.	7, 10, 49
Fluroxene	Fluromar	$F_3C—CH_2—O—CH=CH_2$	12 to 15 per cent (man)	$F_3C—COOH$	Several animals produce trifluoroethanol.	2, 10
Methoxyflurane	Penthrane	$H_3C-O-CF_2—CH—Cl_2$	Approx. 50 per cent (man)	HOOC—COOH F^-	Several other metabolites appear in urine. Nephrotoxicity due to F^-.	28, 39
Enflurane	Ethrane	$HCF_2—O—CF_2—CFClH$	2.4 per cent (man)	HCF_2-O-CF_2-COOH F	Considerably less F than from methoxyflurane.	9
Isoflurane	Forane	$HCF_2–O–CHCl–CF_3$	Very small amount (man)	$F_3C—COOH$, F^-	Minimal release of F^-.	27

tion. However, nitrous oxide is a reactive molecule, and prolonged administration (several days) results in leukopenia.[34] This raises the possibility that nitrous oxide reacts with cellular components. Cohen[10] has suggested that metabolism of nitrous oxide will be demonstrated when radioactive tracers are available.

Cyclopropane

Cyclopropane is a flammable cyclic hydrocarbon. An early report[55] suggested that $^{14}CO_2$ was recovered following ^{14}C-cyclopropane administration, but quantitative studies have not been reported.

Diethyl Ether

"Ether" is a flammable compound whose metabolites are normal cellular constituents. The ether bond is cleaved, forming acetaldehyde and ethanol. These are both metabolized to acetate which enters the carbohydrate and fat metabolic pathways via acetyl-CoA. In mice, approximately 4 per cent of an intravenous dose is transformed.[11]

Chloroform

Chloroform is a nonflammable chlorinated hydrocarbon which is not generally used as an anesthetic in the United States. Recent information about its metabolism has been discussed above. In mice, more than 4 per cent of an administered dose of ^{14}C-chloroform appears as nonvolatile metabolites.[10] The total fraction of chloroform which is metabolized may be much higher. In one study,[46] only 70 per cent of chloroform given to rats was eliminated unchanged by the lungs, suggesting that up to 30 per cent might be metablized. Carbon dioxide is one of the end-products of chloroform biotransformation.

Trichloroethylene

Trichloroethylene (Trilene) is a nonflammable chlorinated hydrocarbon which is used occasionally as an anesthetic for very short procedures. Ten per cent of a dose of trichloroethylene is metabolized to trichloroacetic acid, while another 10 per cent appears as trichloroethanol. The excretion of these products continues for several days following a trichloroethylene anesthetic. Trichloroethanol is itself a sedative drug which can exert a prolonged effect following large or repeated doses of trichloroethylene.[22] Chloral hydrate is no longer thought to be an intermediary metabolite.

Halothane

Halothane (Fluothane) is a nonflammable halogenated two-carbon hydrocarbon. There are three fluorine atoms bonded to one carbon and a bromine and chlorine atom on the other. The metabolites of halothane include bromide, chloride, and trifluoroacetic acid, some of which is excreted as trifluoroacetylethanolamine. The trifluoromethyl group seems not to be cleaved by microsomal enzymes, and fluoride ion is not a metabolite. This stable group is found also in the anesthetics fluroxene and isoflurane. In an early study of halothane metabolism in two

patients, it was found that 12 to 20 per cent of the halothane absorbed during a clinical anesthetic was transformed to urinary metabolites.[49] Another study, in which very small amounts of ^{14}C-halothane were injected intravenously, concluded that up to 25 per cent of the injected dose was metabolized.[7] In this study, male anesthetists metabolized halothane more rapidly than men who did not have occupational exposure to the drug, suggesting microsomal enzyme induction in the anesthetists. In addition, there was a great deal of individual variation in the rate of urinary excretion.

Many cases have been reported in which hepatic dysfunction, including fatal massive hepatic necrosis, occurred in patients following surgery with virtually every known anesthetic. However, in spite of the multiple causes of postoperative jaundice,[33] the term "halothane hepatitis" has been used quite uncritically to describe postoperative hepatic dysfunction, and has even been applied to patients who were later found to have received no halothane. The most convincing evidence that halothane hepatotoxicity exists comes from a few case reports similar to that of Klatskin and Kimberg,[31] in which an anesthetist developed an exacerbation of hepatitis following occupational exposure and following a deliberate subanesthetic exposure to halothane. Speculation concerning the incidence, pathology, and etiology of "halothane hepatitis" has continued for over a decade. The questions may never be answered satisfactorily now that other agents and techniques have reduced the popularity of halothane. Recent reviews[6, 17] have discussed the available studies in depth and should be consulted for details. The Summary of the National Halothane Study[52] reported that the incidence of fatal hepatic necrosis following halothane anesthesia was about 1 per 10,000, and was related more to the death rate of the operation performed than to the anesthetic agent. In fact, the overall death rate following surgery and halothane anesthesia (1.87 per cent) was slightly lower than that following all anesthetics (1.93 per cent). When a second halothane anesthetic occurred within a 2-month period, the incidence of hepatic necrosis was about 7 per 10,000. The question of repeated exposure to halothane has been examined recently in Britian by Inman and Mushin,[29] who concluded that the death rate from hepatic necrosis following more than one exposure to halothane during a 28-day period was about 0.7 per 10,000 patients thus exposed. The pathology of the liver in cases of jaundice following halothane anesthesia is indistinguishable from that of viral hepatitis. It is possible that halothane, given to patients in the incubation stage of viral hepatitis, modifies the usual clinical course of the disease.

Brown[4] has shown that in rats in which microsomal enzymes have been induced, halothane and chloroform cause lipoperoxidation, which could lead to disruption of lipid-rich membranes. In these animals hepatic necrosis followed chloroform, but not halothane anesthesia. Also, enzyme induction led to increased hepatic microsomal protein binding of chloroform, but not of halothane. These observations and the results of a clinical study[23] suggest that the hepatotoxicity of halothane anesthesia is not increased by enzyme induction.

Some clinical aspects of hepatic dysfunction following halothane

anesthesia (including rash, fever, eosinophilia, and "second-set" reaction) suggest a hypersensitive or allergic reaction in which the liver is the target organ. Animal studies have demonstrated the induction of cutaneous hypersensitivity to a halothane metabolite.[36] However, the relationship of these studies to human hepatotoxicity has been questioned.[58]

Fluroxene

Fluroxene (Fluoromar) is trifluoroethyl-vinyl ether. It is flammable in concentrations above 4 per cent in oxygen. In the metabolism of fluroxene the ether bond is cleaved and CO_2 is formed from the vinyl portion of the molecule. As is the case with halothane, the trifluoroethyl group is not degraded.[10] In one study, two men excreted 12 and 15 per cent of an intravenous dose of fluroxene as nonvolatile urinary metabolites.[2] Fluroxene has provided an illustration of the importance of interspecies differences in biotransformation. Although organ toxicity in man is rare following fluroxene anesthesia, the drug is uniformly fatal when given in sufficient (but clinically-relevant) doses to dogs, cats, rabbits, and mice.[8, 30] The underlying pathology is a widespread necrotizing vasculitis.[30] In man the major metabolite of fluroxene is trifluoroacetic acid, while the other species produce trifluoroethanol. The response of animals to trifluoroethanol alone is similar to that of fluroxene in susceptible species. Therefore, the toxicity of fluroxene in these species is due to its species-specific degradation to a toxic metabolite. A case of possible fluroxene hepatotoxicity following enzyme induction in man has been discussed above.

In a subsequent study, Harrison and Smith administered light fluroxene anesthesia in oxygen to rats in which the liver cytochrome P-450 content was increased by phenobarbital pretreatment.[26] Those animals with the highest levels of induced enzyme died of massive hepatic necrosis immediately following anesthesia, while all control animals (those not pretreated with phenobarbital) survived the same anesthetic exposure. Since the livers of the control animals also demonstrated some degenerative changes, fluroxene may be more hepatotoxic to rats than to man. Nevertheless, it would seem wise to avoid fluroxene in patients who have been taking drugs with enzyme-inducing properties.

Methoxyflurane

Methoxyflurane (Penthrane) is a nonflammable halogenated ether. This compound is metabolized to a greater extent (about 50 per cent) than any other volatile anesthetic. One factor contributing to this is its high lipid solubility and correspondingly slow elimination, which prolong the exposure of the anesthetic to the microsomal enzyme system. There are two pathways of methoxyflurane degradation, one involving dechlorination, and the other, cleavage of the ether bond with release of fluoride ion. In addition to chloride and fluoride, methoxydifluoroacetic acid, dichloroacetic acid, oxalate, and formaldehyde are formed.[28] The biotransformation of methoxyflurane results in a dose-related nephrotoxicity,[38] the clinical aspects of which have been discussed in an earlier article. Mazze et al.[38] showed that raising the serum

fluoride level of rats by administration of sodium fluoride results in changes in renal function and histology similar to those seen after nephrotoxic doses of methoxyflurane. It is now generlly agreed that the renal lesion results principally from the fluoride liberated during methoxyflurane degradation.

Van Dyke and Wood[57] have demonstrated in vitro release of inorganic fluoride from methoxyflurane by microsomal enzymes prepared from human and rat livers. The activity of the individual human preparations varied considerably. This may be the basis of the variation in serum fluoride levels reported in humans following similar methoxyflurane anesthetics.[39] Laboratory evidence of renal dysfunction following methoxyflurane anesthesia is seen in patients whose serum fluoride levels exceed 75 μmoles per liter (normal = 1 μmole per 1). Two mechanisms have been suggested by which fluoride might induce high-output renal failure.[38] Fluoride may interfere with cellular energy metabolism to reduce the amount of ATP available to run the sodium pump. This would disrupt the normal renal medullary osmotic gradients and result in polyuria. In addition, fluoride may interfere with the action of antidiuretic hormone (ADH) by inhibiting stimulation of adenyl cyclase by ADH. This would also result in polyuria, which is a prominent feature of methoxyflurane nephrotoxicity.

Enflurane

Enflurane (Ethrane) is a nonflammable halogenated ether. The details of enflurane biotransformation are not known fully, but at least 2.4 per cent of a clinical dose was metabolized in one study of seven women.[9] Both organic and inorganic fluoride were found as urinary metabolities. The small amount of inorganic fluoride found suggests that there is very little cleavage of the ether bond. Dobkin et al. measured the serum fluoride levels of patients who received enflurane anesthesia for major abdominal surgery.[16] The mean concentration of 15.6 μmoles per L found at the end of anesthesia was higher than that found at 24 hours (7.6 μM) and at 48 hours after operation (3.5 μM). The highest serum fluoride level reported in this study, over 40 μmoles per L, was found 24 hours following a 5-hour anesthetic. One case of possible renal dysfunction has been reported following enflurane anesthesia.[35] The patient, who had received a kidney transplant 2 years previously, had a blood urea nitrogen (BUN) of 54 mg per 100 ml before the anesthetic, but her renal condition deteriorated postoperatively. The clinical finding was an inability to conserve water, and was suggestive of the high-output renal failure which can follow methoxyflurane anesthesia. In addition to changes typical of transplant rejection, a kidney biopsy demonstrated some of the pathologic findings of fluoride toxicity. Although this case alone is not proof that the metabolities of enflurane anesthesia can be nephrotoxic, it raised the possibility that a diseased kidney might be more sensitive than normal to fluoride ion, or that it might not be able to excrete a normally innocuous fluoride load. More information is needed about the use of enflurane anesthesia in patients with renal disease.

Isoflurane

Isoflurane (Forane) is a nonflammable halogenated ether. It is a structural isomer of enflurane and has not yet been released for general use.* Although earlier studies had suggested that isoflurane was not metabolized, Hitt et al. have demonstrated its biotransformation in man to trifluoroacetic acid and small amounts of ionic fluoride.[27] Two studies have found peak serum levels of ionic fluoride below 5 μmoles per L following surgical anesthesia with isoflurane,[16, 37] and no evidence of nephrotoxicity was found in a careful study of normal surgical patients who had received the drug.[37] The same study reported that only 10 to 20 per cent as much urinary organic fluoride (presumably trifluoracetic acid) was excreted following isoflurane anesthesia than after a similar exposure to halothane. Isoflurane is metabolized less than any other available halogenated anesthetic.

CONCLUSIONS

The inhalational anesthetics reversibly inhibit mitochondrial electron transport from NADH-linked substrates at the level of the enzyme NADH-dehydrogenase. The effect of this inhibition on ATP production is probably not the basis of the anesthetic state, as the level of high-energy phosphate in the brain does not decrease during anesthesia. Anesthetics, therefore, interfere with brain energy untilization, in addition to brain energy production. Inhibition by anesthetics of mitochondrial calcium uptake, which results from the inhibition of electron transport, may be an important anesthetic effect if it raises the intracellular calcium level. Other areas of investigation which have not been discussed here include the effects of anesthetics on glycolytic and other enzyme systems, ion fluxes, neurotransmitter synthesis and release, and on the structure of natural and artificial membranes.

It is now appreciated that most of the inhalational anesthetics are metabolized by the endoplasmic reticulum of hepatocytes. The biotransformation of several anesthetics can be increased by drugs which induce hepatic microsomal enzymes. The organ toxicities of chloroform, trichloroethylene, fluroxene, methoxyflurane, and possibly of halothane and enflurane are related to their intermediary or final metabolites. It is necessary to keep in mind these principles when considering the choice of anesthetic drugs for an individual patient.

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Effect of Anesthetics and Oxygen Deprivation on Brain Blood Flow and Metabolism

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A great deal of clinically relevant information about the cerebral circulation has accumulated in the past decade. We will review this material. We will first consider cerebral blood flow (CBF) and metabolism in the normal, unanesthetized state; then discuss the effects of anesthesia on CBF; and finally apply this knowledge to several clinical problems.

NORMAL VALUES

Normal values for the cerebral hemodynamic and metabolic variables are summarized in Table 1. These vary with both age and functional state of the brain. Mental activity increases regional cerebral blood volume and presumably regional CBF (rCBF) in active locations. For example, a visual task increases rCBF in the occipital areas.[78] Mean CBF of healthy volunteers was increased during rapid-eye-movement sleep and decreased in slow wave sleep.[103] Oxygen uptake, or metabolic rate for oxygen ($CMRO_2$) is not altered by sleep.[57] Increased CBF has also been observed in cats during both slow wave and rapid-eye-movement sleep.[77]

Mean CBF in a group of children was found to be almost twice that of young adults, and $CMRO_2$ about 25 per cent higher.[11] However, old age by itself does not seem to affect CBF. Arteriosclerotic patients often have reduced CBF, but if these are excluded, there are no differences in CBF or $CMRO_2$ among adults of any age.[52]

Spinal cord blood flow behaves much like CBF. It varies with P_aCO_2, although sensitivity is less than that of brain.[91] Spinal cord blood flow also autoregulates and the lower limit is probably similar to that of brain.[32]

CONTROL OF CBF AND METABOLISM

Effects of Carbon Dioxide

Carbon dioxide has profound effects on cerebral vessels. From P_aCO_2 values of about 25 to 65 torr in man, CBF increases about 1 ml per 100 gm per min for each torr increase in P_aCO_2 (Fig. 1).[46, 47, 76] Within the 25 to 65 torr range, P_aCO_2 has no measurable effect on $CMRO_2$ or the pathways of cerebral carbohydrate metabolism.[2, 47]

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Partly supported through Career Development Award GM 70770-01.

Table 1. *Cerebral Hemodynamics and Metabolism: Normal Values*

VARIABLE	ABBREVIATION	NORMAL VALUES
Cerebral blood flow	CBF	40 to 50 ml per 100 gm per min
Cerebral blood volume	CBV	3.2 ml per 100 gm
Regional cerebral blood flow	rCBF	20 to 80 ml per 100 gm per min
Cerebral metabolic rate for oxygen	$CMRO_2$	3 ml per 100 gm per min
Cerebral metabolic rate for glucose	CMR glucose	4.5 mg per 100 gm per min
Cerebral metabolic rate for lactate	CMR lactate	2.3 mM per 100 gm per min
Cerebral arteriovenous oxygen content difference	$(A\text{-}V)O_2$	6 to 7 ml per 100 ml
Cerebral venous oxygen tension	P_vO_2	35 to 40 torr
Lactate-glucose index	LGI	0 to 10 per cent
Oxygen-glucose index	OGI	90 to 100 per cent
Cerebral tissue concentrations*		
Adenosine triphosphate	ATP	2.36 μM per gm
Adenosine diphosphate	ADP	0.91 μM per gm
Adenosine monophosphate	AMP	0.21 μM per gm
Phosphocreatine	PCr	2.43 μM per gm
Glucose		1.54 μM per gm
Glycogen		2.25 μM per gm
Lactate		2.26 μM per gm

*Values in the mouse;[55] preceding values are for man.[94]

The main control of cerebral vascular tone is exerted by the extracellular fluid (ECF) pH around arterioles.[9, 83, 87] Changes in P_aCO_2 affect CBF very rapidly, because the gas diffuses readily from arterial blood to ECF and changes its pH.[83] Thus, much of the control of CBF is on a local or arteriolar basis. Some investigators believe that the sympathetic nervous system participates in control of the cerebral circulation; this complex subject is beyond our scope, but has been extensively reviewed recently.[9, 75]

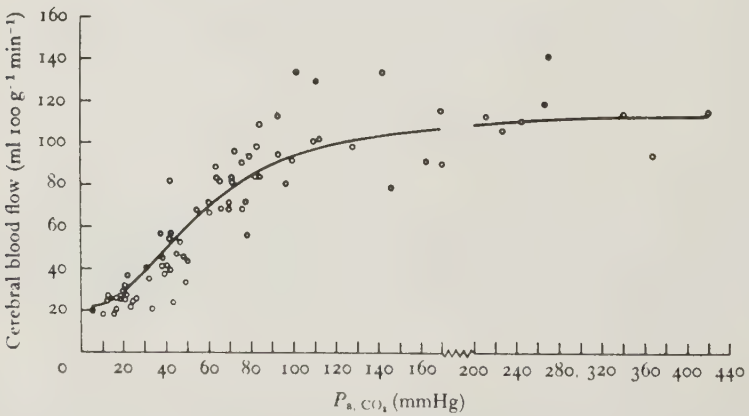

Figure 1. The effect of arterial carbon dioxide tension on CBF in the monkey.[76] (Reproduced from Reivich, M.: Arterial P_{CO_2} and cerebral hemodynamics. Am. J. Physiol., 206:25–35, 1964. Used with permission.)

The limits of cerebral vasodilation are reached at a P_{CO_2} of about 110 torr.[76] At this point, CBF is about 2.5 times its normocarbic value.

The decrease in CBF with hypocarbia is also limited, and in man minimum CBF is reached at a P_aCO_2 of 15 to 20 torr.[107] These half-normal flows probably produce cerebral cellular hypoxia.[3] Although moderate hyperventilation produces few changes, the cerebral metabolic patterns of extreme hyperventilation and arterial hypoxemia are similar (Table 2).[3, 20, 107] In both situations, cerebral glucose consumption and lactate production are elevated; the reduced OGI and increased LGI confirm the shift toward anaerobic metabolism. Cerebral tissue lactate and lactate/pyruvate ratio are also increased by extreme hyperventilation.[34] Furthermore, extreme hyperventilation produces EEG changes and symptoms (dizziness, fainting) similar to those of hypoxemia.[20] Both the metabolic and electroencephalographic abnormalities of hypocarbia can be reversed by hyperbaric oxygenation.[19, 74]

Extreme hypocarbia (P_aCO_2 below 25 torr) should be proscribed. There are, however, some well established indications for more moderate (P_aCO_2 25 to 35 torr) hyperventilation. Its usefulness in control of intracranial pressure and brain size will be discussed elsewhere in this volume.* Many anesthesiologists aver that hypocarbia facilitates control of respiration, improves pulmonary gas transport, prevents atelectasis, and reduces the need for muscle relaxants. The choice of P_aCO_2 for a patient may also be affected by the existence of localized cerebrovascular disease.

Control of CBF in areas *around* a tumor or infarction is sometimes lost. Acid metabolites, e.g., lactate, from the focal abnormal area diffuse into the surrounding tissue. The low pH produces vasodilation and a supranormal flow, which is termed "luxury perfusion;" CBF is high relative to $CMRO_2$, and red (high P_{O_2}) veins may be observed during surgery.[53]

Vasomotor paralysis may also occur *within* focal ischemic areas. These areas are maximally dilated by their own acid production, since flow is inadequate to prevent cellular hypoxia. A paradoxical response of rCBF to inhaled CO_2 is occasionally observed in such regions:[12, 34] the increased P_aCO_2 dilates normal vessels, but those in the ischemic region are already maximally dilated. Since resistance has decreased in normal areas and has remained unchanged in ischemic areas, blood is effectively shunted from ischemic to normal tissue. This phenomenon has been termed the "intracerebral steal syndrome."[34] The "inverse steal" or "Robin Hood" syndrome has been observed in response to hypocarbia: in response to lowered P_aCO_2 normal vessels constrict but hypoxia keeps the ischemic vessels maximally dilated.[54]

It is important to note that luxury perfusion, steal, and inverse steal occur inconsistently in patients with regional flow abnormalities. Moreover, one cannot predict *a priori* whether rCBF will respond appropriately or paradoxically to a P_{CO_2} alteration. Therefore, the rationale of treating focal ischemia with extremes of either hypocarbia or hypercarbia for the purpose of inducing or preventing steals is questionable.

Oxygen Delivery

The effects of moderate, acute hemodilution on cerebral hemodynamics are surprisingly small. In a well controlled animal experiment, moderate reduction in hemoglobin to 7.8 gm per 100 ml had no effect on $CMRO_2$ and little on CBF. Severe hemodilution had pronounced effects. Results suggested that anaerobic metabolism was taking place.[60]

The effects of arterial hypoxemia on cerebral hemodynamics are similar to those of normoxic anemia (see Table 2). As P_aO_2 is decreased in normal man (at constant P_{CO_2}), there are initially no changes in CBF or $CMRO_2$; however, as P_aO_2 is further lowered to 50 torr, cerebral vasodilation begins and at P_aO_2 of 35 torr, a 51 per cent increase in CBF was reported with a suggestion of anaerobic metabolism.[20] The mechanism of hypoxic vasodilation is uncertain, but accumulation of acid metabolites in periarteriolar ECF is probably involved.

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* See Shapiro and Aidinis, "Neurosurgical Anesthesia."

Table 2. *Effects of Hyperventilation and Hypoxemia on Cerebral Blood Flow and Metabolism*

VARIABLE	UNITS	NORMAL CONTROL	AWAKE HYPOXEMIA	70 PER CENT N_2O MODERATE HYPERVENTILATION	70 PER CENT N_2O EXTREME HYPERVENTILATION
P_aO_2	torr	100	35	150	190
P_aCO_2	torr	38	39	19	10
CBF	ml per 100 gm per min	44	77	25	21
$CMRO_2$	ml per 100 gm per min	3.01	3.10	3.02	2.76
CMR glucose	mg per 100 gm per min	4.50	5.7	4.2	4.8
CMR lactate	mM per 100 gm per min	2.30	10.7	4.5	9.3
OGI	per cent	92	76	85	77
LGI	per cent	6	19	6	17
P_vO_2	torr	36	27	19	17
References	—	20	20	3, 107	3, 107

Carbon dioxide has such a pronounced effect on cerebral vessels that it is not surprising to find that P_aCO_2 modifies the effects of hypoxia on CBF. If hyperventilation is permitted to occur in response to hypoxia, the resultant hypocarbia opposes the dilating effect of hypoxia and CBF may not increase until P_aO_2 is below 35 torr.[18]

Oxygen is a very mild cerebral vasoconstrictor; a decreased CBF is barely detectable when breathing 100 per cent oxygen at 1 atmosphere absolute pressure.[89] The effect becomes more pronounced during hyperbaric oxygenation; at 2 atmospheres absolute CBF was reduced 21 per cent from the normoxic state.[38]

Autoregulation

"Autoregulation" refers to an organ's ability to maintain flow constant in the face of alterations in perfusion pressure. Perfusion pressure is the difference between mean arterial and mean venous pressure. In the presence of a space-occupying lesion, cerebral venous pressure may not reflect a raised intracranial pressure. Perfusion pressure would then be better represented by the difference between mean arterial and intracranial pressures.[41] The capacity to autoregulate is present to a remarkable degree in brain. CBF is held virtually constant over the perfusion pressure range of 60 to more than 150 torr.[51] At very low arterial pressure, the limits of cerebrovascular dilation are reached and autoregulation fails. CBF decreases and clinical signs of ischemia (nausea, fainting, dimmed vision, etc.) occur when mean arterial blood pressure is 48 to 55 torr.[28, 66] At lower pressures brain tissue death is imminent. An upper limit of autoregulation has been demonstrated in animals.[40, 99] Autoregulation "breakthrough" during high arterial pressure is characterized by cerebral edema and intracerebral hemorrhage. Perhaps autoregulation breakthrough plays a role in the pathophysiology of hypertensive encephalopathy.

The mechanism of autoregulation is controversial. Autoregulation may occur as a consequence of myogenic reflexes of vascular smooth muscle in response to changes in transmural pressure[75] or, alternatively, metabolic control might operate to keep ECF pH constant.[9, 84] A pressure-induced increase in CBF, for example, would transiently increase CBF, wash out carbon dioxide, raise ECF pH, and then induce compensatory vasoconstriction.

Autoregulation is disturbed in certain disease states. Global loss of autoregulation can follow grand mal seizures[73] and also appears locally in and around areas of cerebral ischemia and tumors.[27] Strong vasodilatory stimuli such as hypoxia or hypercarbia also disrupt autoregulation.[27, 88] Of importance clinically is the fact that the pressure range of CBF constancy is reduced in chronic hypertension.[26] This accords with the observation that symptoms of ischemia may appear in chronic hypertensives with only modest arterial blood pressure decreases.

Temperature Changes

Cerebral oxygen consumption is dependent on body temperature (Fig. 2). $CMRO_2$ is approximately halved at a body temperature of 30° C[8] and fever elevates $CMRO_2$.[69] Changes in flow match those of oxygen consumption so that $CBF/CMRO_2$ and venous Po_2 are little affected by temperature.[94] The decreased $CMRO_2$ of hypothermia is protective; the *estimated* period of "safe" circulatory arrest is increased from 3.5 min at 37° C to 10 and 31 min at 30° C and 19° C respectively.[8] Conversely, cerebral ischemia or hypotension is more dangerous in the febrile patient.

Cerebral Blood Volume

The normal cerebral blood volume (CBV) in man is 3.2 ml blood per 100 gm brain.[33] Cerebral blood volume varies with CBF, so that an increase in CBF will result in raised CBV.[93] These CBV alterations may affect intracranial pressure.

CEREBRAL METABOLIC PATHWAYS AND THE QUANTIFICATION OF HYPOXIA

Glucose, the primary (and usually sole) energy source of the brain, is converted to pyruvate by glycolysis. Under normoxic conditions most of the pyruvate

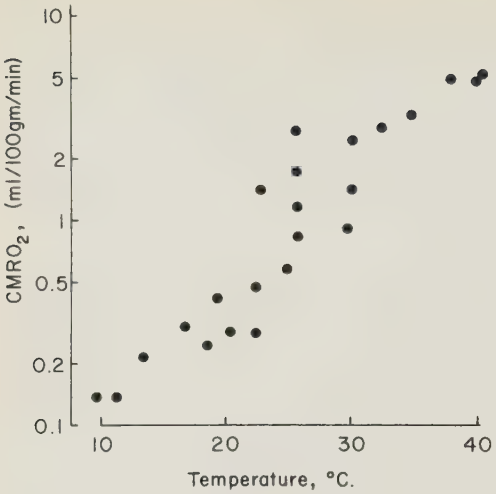

Figure 2. Relationship between body temperature and $CMRO_2$. (Reproduced from Bering, E. A.: Effects of profound hypothermia and circulatory arrest on cerebral oxygen metabolism and cerebrospinal fluid electrolyte composition in dogs. J. Neurosurg. 39:199–205, 1974. Used with permission.)

is metabolized in the Krebs cycle to CO_2 and H_2O; each mole of glucose then yields 38 moles of high energy phosphate in the form of adenosine triphosphate (ATP).[56] Operation of the Krebs cycle requires the participation of oxygen as an electron acceptor. During conditions of reduced oxygen delivery, cerebral tissue can obtain energy from the anaerobic reduction of pyruvate to lactate.[20] This process is less efficient, yielding only 2 moles of ATP per mole of glucose, and cannot itself maintain cerebral tissue in a viable state. Normally, 95 per cent of glucose is oxidatively metabolized to carbon dioxide and water, and only about 5 per cent to lactate.[2, 20] These percentages are called the oxygen-glucose index (OGI) and lactate-glucose index (LGI) respectively.

Essentially no cerebral oxygen storage is possible and stores of high energy phosphates in the form of ATP, ADP, and phosphocreatine (PCr) are sufficient to maintain tissue viability for only a few minutes.[55, 86] Since the brain is exquisitely sensitive to loss of its oxygen supply, it is of great interest to be able to quantify the severity of an hypoxic stress.

The adequacy of cerebral oxygen supply may be estimated from the ratio of blood flow to oxygen consumption, $CBF/CMRO_2$.[95] $CBF/CMRO_2$ equals $1/(A\text{-}V)O_2$ and is thus easily measured. Cerebral venous Po_2 (P_vo_2) is a measure of tissue oxygenation and is also a function of $CBF/CMRO_2$; increases in CBF or decreases in $CMRO_2$ elvate P_vo_2. Unfortunately, neither P_vo_2 nor $CBF/CMRO_2$ is very sensitive to small focal abnormalities.[50] There is a so-called "critical" P_vo_2 of about 20 torr, below which tissue hypoxia probably occurs.[94]

Because the anaerobic pathway is inefficient, its use during low oxygen states results in more glucose being metabolized to obtain an equivalent amount of ATP. Thus, a rising glucose consumption (CMRglucose) in the presence of an apparently constant or slightly falling $CMRO_2$ suggests cellular hypoxia. Similarly, hypoxia results in an increased lactate production (CMR lactate), an increased cerebral venous lactate/pyruvate ratio, an increased LGI, and a decreased OGI.[20] Lactate may also appear in the cerebrospinal fluid.

INHALATION ANESTHETICS

Effects on CBF

The effects of many of the common inhalation anesthetics on CBF in man are shown in Table 3. Seventy per cent nitrous oxide, with or without thiopental induction, had little or no effect.[92, 106, 107] However, this agent is not sufficiently po-

Table 3. *Effects of Anesthesia on Cerebral Blood Flow and Metabolism in Normocarbic Man*

ANESTHETIC	MAC* MULTIPLE	CBF ml per 100 gm per min	CBF PER CENT CHANGE FROM CONTROL	$CMRO_2$ ml per 100 gm per min	$CMRO_2$ PER CENT CHANGE FROM CONTROL	REFERENCES
None—awake	0	44.4	–	3.09	–	20, 94
N_2O 70 per cent, thiopental induction	.7	40.5	9	2.39	−23	2, 106
N_2O 70 per cent, thiopental induction	.7	45.4	+1	3.02	−2	3, 107
N_2O 70 per cent, no thiopental	.7	45.4	+2	2.38	−23	92
Cyclopropane 5 per cent	.5	26.2	−36	1.68	−40	4
13 per cent	1.2	34.3	−25	2.27	−29	94, 110
20 per cent	1.8	66.0	+61	2.50	−30	94, 110
37 per cent	3.4	75.6	+66	2.24	−34	94, 110
Diethyl ether 2.4 per cent	1.2	38.8	−6	1.75	−34	108
4.5 per cent	2.2	67.5	+36	2.24	−12	108
Halothane 1.2 per cent	1.5	50.8	+14	2.80	−9	15, 17, 105
1.2 per cent	1.5	54.4	+27	2.19	−26	15, 17, 105
Enflurane 0.85 per cent	.5	39.0	−5	2.28	−25	94, 109
2.0 per cent	1.2	40.6	+2	2.06	−33	94, 109
3.0 per cent	1.8	40.0	−3	1.53	−50	94, 109
3.2 per cent	2.0	40.8	+2	1.84	−40	94, 109
Thiopental 35 mg per kg	–	27.6	−48	1.5	−54	71

*MAC or minimum alveolar concentration is the concentration of anesthetic required to prevent movement in response to a surgical skin incision in 50 per cent of patients. MAC multiple is defined as existing concentration ÷ MAC.

tent by itself to produce general anesthesia in most patients. The older, flammable anesthetics produce different results. Cyclopropane, for instance; has a biphasic effect in normocarbic man, with subanesthetic doses, and light anesthesia caused depressed CBF.[92, 94] However, moderate and deep anesthesia markedly increased CBF. It is likely that this is due to an interaction between the direct effects of the agent and the catecholamines that are released during cyclopropane anesthesia.

Diethyl ether affects the cerebral circulation like cyclopropane (see Table 3). There was a small decrease in CBF during light ether anesthesia and a large increase during deep anesthesia.[108] Perhaps catecholamine release also plays a part in ether's cerebral hemodynamic effects.

Halothane (Fluothane) increases cerebral blood flow at all clinically useful doses (Table 3, Fig. 3).[102, 105] The increases are significant, but not as marked as with the flammable agents.

Enflurane (Ethrane) increases CBF in the dog; the magnitude of change is similar to that of halothane.[65] Studies in man suggest that enflurane does not alter CBF.[94, 109] The disagreement might be explainable on the basis of species difference, but blood pressure changes might also be a factor. Enflurane is a circulatory depressant and arterial blood pressures in the healthy men that volunteered for the CBF study were lower than would be permitted in the typical surgical patient. Although autoregulation is intact during anesthesia, the supranormal CBF of a vasodilating anesthetic might not be sustained during hypotension.[92] The limits of cerebrovascular dilation are reached at higher arterial pressure levels when vessels are already dilated by a drug. It is probable, therefore, that CBF would be elevated in a normotensive surgical patient anesthetized with enflurane.

Methoxyflurane (Penthrane) also increases CBF (see Fig. 3).[63] Isoflurane (Forane) is a potent dilator of cerebral vessels.[21] We can make the generalization that all of the halogenated anesthetics in common clinical use increase CBF.

The responsiveness of CBF to P_aCO_2 alterations is essentially unchanged during 70 per cent nitrous oxide inhalation.[106] However, the more potent anesthetics increase CBF-P_aCO_2 responsiveness.[1]

Responsiveness of CBF to P_aCO_2 may be more closely related to anesthetic dose, than to the particular agent used. Figure 4 shows that the slope of the P_aCO_2/CBF response is almost the same for four different halogenated anesthetics at equivalent dose.[65]

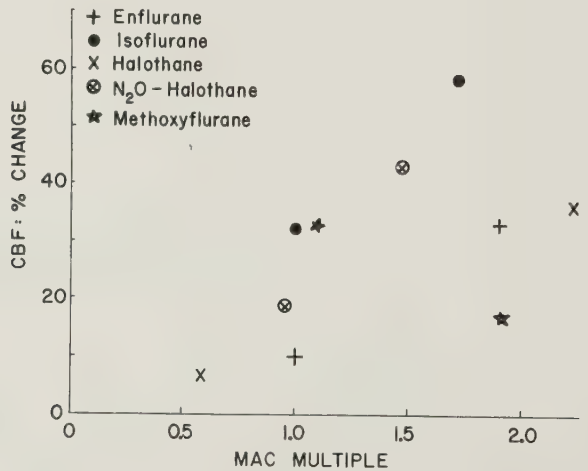

Figure 3. Effects of anesthetic dose, in multiples of MAC, on canine CBF.[21, 63, 65, 102]

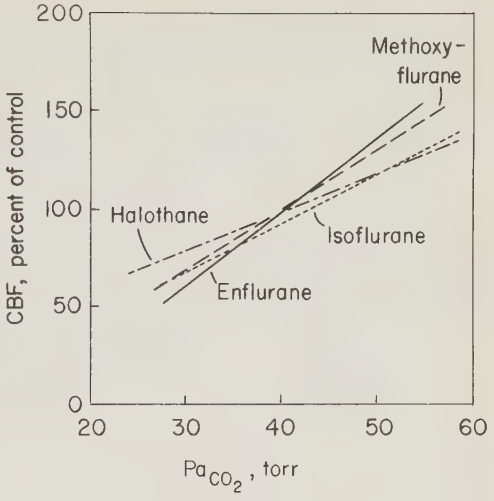

Figure 4. Response of CBF to P_aCO_2 alterations during light anesthesia in dogs. (Adapted from Michenfelder, J. D., and Cucchiara, R. F.: Canine cerebral oxygen consumption during enflurane anesthesia and its modification during induced seizures. Anesthesiology, 40:575–580, 1974.)

Effects on Cerebral Metabolism

Brain oxygen consumption is reduced by all of the inhalation anesthetics (Table 3, Fig. 5). Seventy per cent nitrous oxide decreases $CMRO_2$.[92, 106, 107] $CMRO_2$ during both diethyl ether and cylcopropane administration was less during light anesthesia than deep anesthesia.[94, 108] A metabolic stimulating effect of catecholamines might have limited the fall in $CMRO_2$ that deeper anesthesia would otherwise have produced. Light anesthesia with either halothane, methoxyflurane, or isoflurane causes a moderate fall in $CMRO_2$.[17, 21, 63] Enflurane produces a profound $CMRO_2$ reduction in man (see Table 3).[109] It is unlikely that hypotension could have affected this observation significantly.

None of the halogenated anesthetics alters the normal pattern of cerebral glucose metabolism.[94] However, 5 per cent cyclopropane administration in man was associated with increased brain lactate production but was not present during deeper anesthesia.[4] It would be interesting to know whether clinically significant cerebral hypoxia was produced, since low cyclopropane concentrations are present in the brain at least transiently during induction and emergence.

Anesthesia with diethyl ether, halothane, enflurane, or methoxyflurane (and probably others) increases cerebral tissue energy reserves as much as 1.7 times the awake value.[14] The increase is mostly due to glucose and glycogen; little or no increase in high energy phosphate compounds occurs.

Anesthetics and Cerebral Circulatory and Metabolic Control

There seems to be no uniformity among the inhalation anesthetics in degree of $CMRO_2$ depression or direction and magnitude of CBF alteration. However, consistency improves when we consider the ratio $CBF/CMRO_2$, the quantity of blood flow available per unit oxygen consumption. There is a clear trend for $CBF/CMRO_2$ to increase with increasing anesthetic depth, providing a higher tissue and venous Po_2. In fact, cerebral venous Po_2 is the same for all of the inhalation agents at equivalent anesthetic dose (MAC multiple).*[93] The increased cerebral venous Po_2 might indicate an improved safety margin, but clinical evidence does not support this hypothesis.

*Minimum alveolar concentration (MAC) is the alveolar anesthetic concentration required to prevent movement in response to a surgical incision in 50 per cent of patients. MAC multiple is the alveolar anesthetic concentration divided by MAC.

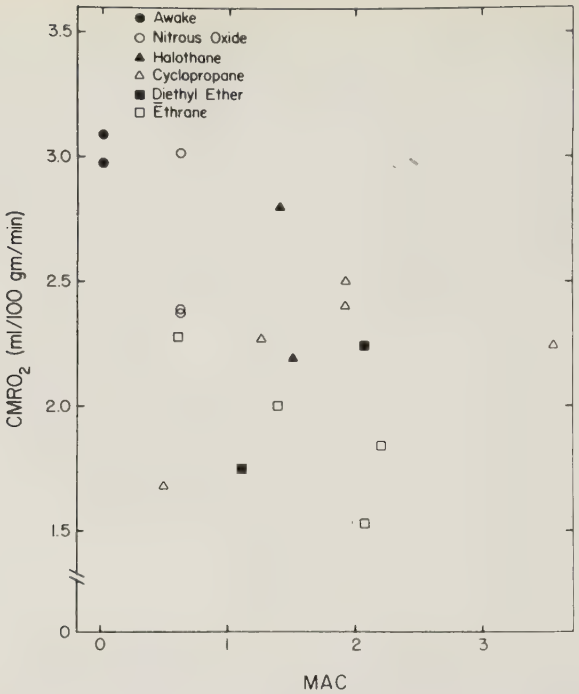

Figure 5. Effects of anesthetic dose, in multiples of MAC, on human $CMRO_2$.[94] (Reproduced from Smith, A. L., and Wollman, H.: Cerebral blood flow and metabolism.: Effects of anesthetic drugs and techniques. Anesthesiology, 36:378–400, 1972. Used with permission.)

A speculation on the mechanism of this phenomenon is that anesthetics reset the level of cerebral blood flow control. Perhaps the brain "wants" a higher tissue Po_2 or pH; this would be reflected in an increased cerebral venous Po_2. The logical consequence of this theory is that CBF alterations during anesthesia are not due primarily to direct effects on vascular smooth muscle. Rather, the anesthetic depresses $CMRO_2$ and resets flow control. Evidence supporting this theory was obtained in dogs.[97]

INTRAVENOUS ANESTHETICS AND ADJUVANTS

Barbiturates

Sedative doses of the commonly used barbiturates, which do not cause loss of consciousness, have no effect on CBF or $CMRO_2$,[45] but anesthesia with thiopental markedly decreases both CBF and $CMRO_2$. In normocarbic men anesthetized with a large dose of thiopental, 35 mg per kg, both CBF and $CMRO_2$ were halved.[71] Hyperventilation further reduced mean CBF to an extremely low value. It is likely that this action is common to all barbiturates. Acute tolerance to the anesthetic effects of thiopental is well known. Besides decreasing CBF, barbiturate anesthesia lessens the rCBF differences which are usually found in the awake state.[49]

Narcotics and Narcoleptics

The cerebral circulation is not affected by small, premedicant doses of narcotics, as long as Pco_2 is not elevated.[89] A larger dose of morphine, 20 to 30 mg subcutaneously, also had negligible effect.[58] Sixty mg intravenously, a dose al-

most in the anesthetic range, elevated CBF in a group of normal men.[67] However, ventilation was spontaneous, and the increase may have been due to an elevated P_{CO_2}. $CMRO_2$ in these subjects fell 41 per cent from control; it is unlikely that P_{CO_2} would have affected this measurement. The metabolic depression of morphine can be partially reversed by n-allylnormorphine (Nalline)[67] and could presumably be reversed even more completely by naloxone (Narcan). Depression of CBF and $CMRO_2$ is proportional to the dose in dogs, although increasing the dose above 1.2 mg per kg gives little additional effect.[101]

As with the narcotics, premedicant doses of neuroleptics do not affect cerebral hemodynamics. Droperidol (5 mg) plus phenoperidine (1.5 mg) did not alter CBF in man.[6] A study of nitrous oxide plus fentanyl (Sublimaze) and/or the neuroleptic droperidol (Inapsine) showed that 15 minutes after 0.006 mg per kg of fentanyl had been given intravenously, CBF was decreased 46 per cent and $CMRO_2$ was decreased 18 per cent.[62] Droperidol 0.3 mg per kg lowered CBF 40 per cent but did not alter $CMRO_2$. Innovar, a combination of these drugs, was associated with 50 per cent and 23 per cent decreases in CBF and $CMRO_2$ respectively.

There is no evidence to suggest that narcotics are hazardous to the diseased cerebral circulation.

Ketamine

Ketamine is the only anesthetic that increases $CMRO_2$. With background nitrous oxide anesthesia, $CMRO_2$ is increased by 16 per cent and CBF 80 per cent by 2 mg per kg of ketamine. The drug is short acting, so that these values returned to normal 20 to 30 minutes after administration. The increase in CBF could be prevented by giving thiopental before the ketamine.[22, 100]

Vasoactive Drugs

Epinephrine, given intravenously in large doses, elevated CBF and $CMRO_2$ in man.[48] Smaller doses have no significant effect.[94] Norepinephrine (Levophed) and metaraminol (Aramine) appear to be mild cerebral vasoconstrictors, but neither affects $CMRO_2$.[68] Either of these drugs will correct the low CBF of severe hypotension, but because of the cerebral vasoconstriction, blood pressure must be slightly elevated to obtain a normal CBF. Neither angiotensin nor phenylephrine affects CBF or $CMRO_2$ in normal man.[92]

Local Anesthetics

Cerebral hemodynamics of man were not altered by 750 mg procaine, given by intravenous drip over a 20 min period.[81] The effects of liodcaine have been studied in dogs.[80] A 15 mg per kg intravenous bolus depressed $CMRO_2$ 27 per cent 2 minutes after administration; $CMRO_2$ returned to control after 60 minutes. Lidocaine-induced seizures were associated with a nonsignificant elevation of $CMRO_2$. The drug produced small or no decreases in CBF.

ANESTHETIC EFFECT IN OXYGEN DEPRIVATION

Anesthetic effects in oxygen deprivation are of considerable interest, since barbiturates may have a protective effect. The metabolic and pathologic response of the brain to low oxygen states depends on whether arterial hypoxemia, ischemia, or both are present. Although oxygen delivery is impaired in both situations, glucose delivery and clearance of acid metabolites are decreased only in ischemia, and the time course of the insult is often important; for example, after 3 minutes of breathing 5 per cent oxygen, tissue glucose and phosphocreatine levels are decreased, but they are back to normal after 30 minutes.[23]

Metabolic Effects

When severe hypocapneic hypoxemia was produced in dogs, brain tissue ATP level fell and lactate increased.[64] The EEG changes observed could be delayed by prior administration of thiopental, but the drug did not mitigate the metabolic abnormalities.

Although not observed in hypoxia, a salutary metabolic effect of barbiturates may occur in cerebral ischemia. Both severe hypotension and hypoxemia result in a depletion of cerebral energy stores. Nitrous oxide does not prevent this depletion, but it is less severe in animals given barbiturate anesthesia.[70]

Hypothermia prolongs the time during which the brain will tolerate complete ischemia.[8, 37] Hypothermia also slows the cerebral energy reserve depletion, whereas the volatile anesthetics probably do not.[61] Thus, the decreased $CMRO_2$ in hypothermia not only results in a decrease in the amount of oxygen required for brain function, but also reduces the amount necessary to maintain cellular integrity.

Barbiturate Protection in Infarction

Protection of the oxygen-deprived brain by barbiturates was suggested more than 10 years ago. Several laboratories subjected animals to severe hypotension and/or hypoxemia. Barbiturate anesthesia decreased the resulting neurologic sequelae or increased survival time.[16, 111, 111] These studies are important contributions, but must be interpreted cautiously. Severe anoxia and total cerebral ischemia produce major cardiovascular alterations, which could affect the likelihood of insult. Since anesthetics modify the cardiovascular responses to hypoxemia, acidosis, and the recovery from hypotension, it is difficult to assess the degree of baributrate protection which might have resulted from salutary effects on other organ systems.

My colleagues and I have studied barbiturate protection from regional cerebral ischemia in dogs and baboons subjected to unilateral, permanent middle cerebral artery occlusion. We maintained normal arterial pH, Po_2, Pco_2, and blood pressure in all animals. "Awake" dogs and animals of both species anesthetized with halothane developed large infarctions and hemiparesis. Dogs pretreated with a moderate dose of thiopental or pentobarbital or given thiopental 15 minutes after vessel occlusion suffered little or no infarction.[35, 98] Infarction size was significantly reduced in the baboons by pentobarbital, but large doses were required. Because of the high dose requirement in primates, clinical use of barbiturate therapy in treatment of acute stroke must await further animal research.

IATROGENIC CEREBRAL ISCHEMIA

Anesthesia for Carotid Endarterectomy

Patients about to undergo carotid artery surgery are often elderly and hypertensive, and may have generalized arterial disease as well. If arterial occlusion without a shunt is necessary, the remaining vessels, which are often stenotic themselves, must supply the territory of the occluded artery. Anesthetic management by judicious choice of anesthetic drug, control of blood pressure, and control of Pco_2, can reduce the chance of a permanent neurologic deficit.

Hypercarbia increases CBF in normal brain. However, it also occasionally causes steals, worsening ischemia.[12, 54] In animals subjected to middle cerebral artery ligation, higher Pco_2's were associated with larger infarctions;[7, 90] however, this is not a consistent finding.[113] Animal studies indicate that cerebral ATP content in ischemia is lower during hypercarbia than normocarbia.[25]

The possible benefit of lowering Pco_2 is suggested by several clinical studies. Both rCBF and stump pressure were studied during carotid endarterectomy.[11] Hypercapnia, as opposed to normocapnia or hypocapnia, was associated with decreases in both stump pressure and efficiency of autoregulation. Furthermore, intracerebral steals from the ischemic regions were found in 24 per cent of patients during hypercarbia. Other workers have confirmed the finding of steals during carotid clamping and raised Pco_2.[72] In a third study, stump pressure was measured at several Pco_2 levels in each patient during carotid clamping.[30] In most patients the highest stump pressures were associated with the lowest Pco_2 values. Unfortunately, the situation is not completely clearcut: there are reports in the literature of two patients whose stump pressure or ischemic rCBF were worsened by hyperventilation.[13, 30] We have also seen that extreme hyperventila-

tion (Pco_2 = 20 torr) produces cerebral metabolic changes that resemble those of hypoxemia. I would therefore suggest that moderate hyperventilation to a Pco_2 of no less than 30 torr be used. At this Pco_2 level, both steals and hypocarbic cerebral hypoxia should be prevented. An arterial Pco_2 of 30 to 35 torr is clearly a compromise, designed to benefit most patients and harm few. At present, there is no way to know a priori which patients will develop steals and which will not. Only when we have the ability to clinically measure local circulatory adequacy will it be possible to determine which Pco_2 level is ideal for each patient.

The choice of anesthetic technique first requires the choice of local or general anesthesia. Local anesthesia has the advantage of making neurologic symptoms immediately obvious if they develop during carotid clamping. However, we have seen evidence that general anesthesia improves tolerance to cerebral ischemia. Furthermore, some patients may tolerate a short test occlusion but not an occlusion long enough for endarterectomy.[10] Also, Pco_2 and Po_2 are difficult to control during local anesthesia.

If general anesthesia is employed, which agents are best? It is probably *not* worthwhile to choose the agent that depresses $CMRO_2$ most. The differences in $CMRO_2$ reduction among the volatile agents are small, and we do not even know that a reduced $CMRO_2$ is beneficial (see Fig. 5). It has been suggested that the lowered $CMRO_2$ of the volatile anesthetics represents decreased function, not a decrease in the amount of oxygen required to maintain cellular integrity.[61] Although barbiturates may have a protective effect in cerebral ischemia, more work needs to be done before this phenomenon can be applied clinically. Should we choose the anesthetic that most increases CBF? Animal studies produce no evidence that the cerebral vasodilation of halothane causes intracerebral steals,[96] but this possibility has not been studied in man. Of course, the studies of stump pressure and rCBF during carotid clamping that we discussed earlier suggested that the cerebral vasodilation of hypercarbia might be deleterious. Also, infarctions in our middle cerebral artery occlusion studies in the dog were worse with deep halothane than with light; this was probably due to the cerebral vasodilation of deep halothane.[98] It seems reasonable, then, to choose an anesthetic technique which will produce the fewest effects on cerebral hemodynamics. Furthermore, the anesthetist should employ a regimen which in his own experience results in the best cardiovascular stability in these fragile patients. Nitrous oxide, supplemented with small amounts of either thiopental, narcotics, halothane, or enflurane, would seem to be a reasonable choice.

There is more agreement on the question of blood pressure support than on choice of Pco_2 or anesthetic. Both salutary and adverse effects of raising blood pressure have been reported on rCBF in animals subjected to middle cerebral artery occlusion.[7, 104] Clinically, induced hypertension has elevated rCBF and stump pressure distal to the clamped carotid and has reversed neurologic symptoms of cerebral ischemia.[26, 30, 72] Most workers would employ a vasopressor such as phenylephrine or metaraminol to keep mean arterial blood pressure during clamping at or above ward level. If stump pressure is inadequate, arterial pressure may be further increased and another measurement of stump pressure made.

Both hyperbaric oxygenation[36, 39] and hypothermia[79, 112] have been proposed for use in carotid surgery. The former technique improves oxygen delivery during a period of reduced CBF and the latter increases tolerance to cerebral ischemia. Unfortunately, very few centers have facilities for hyperbaric surgery, and the disadvantages of hypothermia are that it prolongs anesthesia time and has its own morbidity. Complications of hypothermia include cold damage to skin, altered blood coagulation, and cardiac arrhythmias. It would seem, then, that hyperbaric oxygenation and hypothermia are to be reserved for the patient with unusually severe disease or with an unusual problem.

Deliberate Hypotension

Induced hypotension is employed to reduce bleeding and brain size and to facilitate surgery on the circle of Willis. The nonanesthetic drugs commonly used for hypotension have little or no direct effects on CBF or $CMRO_2$.[89] Autoregula-

tion is intact during general anesthesia and maintains CBF almost constant over a wide range of pressures. Signs of cerebral ischemia occur in normal, awake man at mean arterial blood pressures in the range of 48 to 55 torr (systolic pressure about 60 to 70 torr).[28, 66] Apparently, anesthetized patients tolerate even lower pressures. In two studies of anesthetized patients with mean arterial pressure below 50 torr,[24, 82] no patient of either group suffered permanent neurologic or psychologic deficits, and the lowest cerebral venous Po_2 observed was 27 torr. This latter observation must be interpreted cautiously; the cerebral venous Po_2 values were in a range not associated with cerebral tissue hypoxia, but this measurement averages out values for the whole brain and is not useful for predicting the occurrence of focal ischemia.[50] It is important to note also that these were patients free of occlusive cerebrovascular disease; one would not expect induced hypotension to be as safe in the older, arteriosclerotic patient.

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Neuromuscular Blockade

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Neuromuscular blocking drugs are an integral part of anesthetic practice with a steadily increasing safety record. The reasons for this are several. This review will survey recent developments that are of importance in the safe and rational use of relaxants. The antagonism and recovery from neuromuscular block is more completely understood. There is greater appreciation of the many factors that may alter relaxant effects, especially those common to everyday anesthetic management. The complications of depolarization have been defined. Monitoring the degree of neuromuscular block has proven to be a useful clinical technique increasing the precision of relaxant administration. A new agent, pancuronium bromide, more closely approaches the theoretical ideal relaxant and thus is a significant new drug.

DEPOLARIZERS AND NONDEPOLARIZERS

The division of relaxants into depolarizing and nondepolarizing groups is an oversimplification since prejunctional effects of relaxants and differences in mechanisms within the groups have been demonstrated.[22,23,72] Such a classification is, however, useful in a discussion of clinical use. Among various distinguishing features between the two groups is the response of muscle to peripheral nerve stimulation; this response has direct application in the clinical monitoring of relaxant effects. With the nondepolarizing relaxants, d-tubocurarine, gallamine, and pancuronium, a decreasing height of the action potential or the mechanical response following a single, supramaximal stimulus delivered every few seconds (twitch response), a fade during the delivery of tetanic rates, commonly 30 H_z or greater, and an increase in the response to greater than the preceding twitch height when the slower rate is applied following a tetanus (post-tetanic facilitation) are seen. The block is antagonized by anticholinesterase administration.

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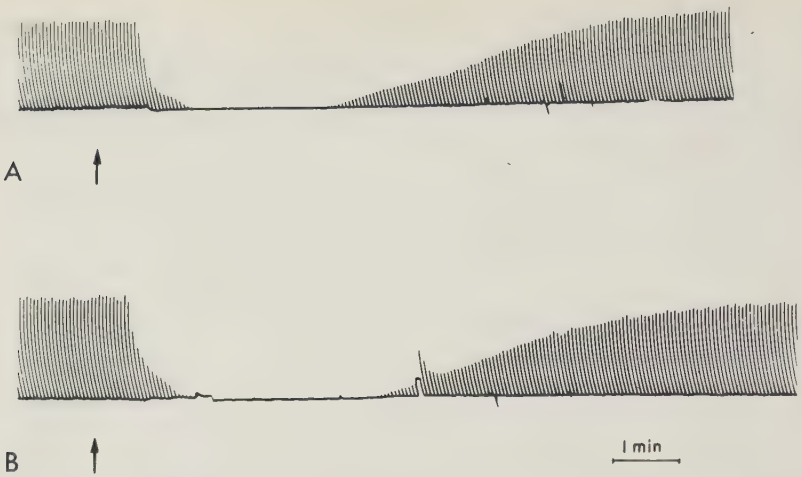

Figure 1. Characteristics of (*A*) deplorization and (*B*) desensitization block following succinylcholine 0.5 mg/Kg. Panel *A* shows the response of the first injection and Panel *B*, the eleventh injection. Note the similar recovery time. (Reproduced from Katz, R. L., and Ryan, J. F.: Neuromuscular effects of succinylcholine in man. Br. J. Anaesth., *41*:381–309, 1969. Used with permission.)

The depolarizing drugs include succinylcholine and decamethonium, although decamethonium is now rarely used. Characteristics of a depolarization block are a decrease in action potential or mechanical response, no fade with tetanus, and lack of post-tetanic facilitation (Fig. 1). The block is potentiated by acetylcholine or anticholinesterase administration. Depolarization of the postjunctional membrane with a reduced sensitivity of the electrically excitable adjacent muscle membrane is the initial mechanism of block.[87] Gradual repolarization of the postjunctional membrane occurs; but with an increase in the dose of depolarizers and increasing time of administration, a decreased sensitivity of the membrane to acetylcholine develops.[29] This desensitization develops earlier and more frequently during the use of these agents than previously recognized.[6, 48, 49] With desensitization, fade with tetanus and post-tetanic facilitation are seen although the facilitation is not as great as seen with nondepolarizing relaxants (see Fig. 1).

MODERN METHODS OF ADMINISTRATION

During surgical procedures, the degree of neuromuscular block achieved with relaxants varies depending upon the requirements of the operation and the inhalational anesthetic used. During abdominal procedures, adequate relaxation can usually be achieved by a 75 to 90 per cent depression of function of the nerve muscle junction (twitch height) when light levels of anesthesia are used, and by less depression during deeper anesthesia.[14, 42] The use of 90 per cent depression as a maximal value, except for short periods of time, is important in avoiding overdose and assuring prompt recovery either spontaneously or with the aid of antagonists.

Both the intensity and duration of block are altered by many factors. Wide variation in intensity and duration of block have been described with all relaxants in individuals who are without conditions known to alter neuromuscular function. The use of d-tubocurarine 0.1 mg per kg eliminates the twitch response in some patients, does not alter the response in others, and produces an intermediate degree of depression in most.[40] Similarly, succinylcholine infusion rates necessary to maintain a 90 per cent depression of twitch vary from 1.7 to 15.2 mg per kg per hour.[48] Because of the variation in response and the many factors altering block, test doses are frequently used when nondepolarizing agents (d-tubocurarine 3 mg, gallamine 20 mg, pancuronium 0.5 mg) are administered; test doses of depolarizing drugs are rarely used.

The most precise way of monitoring relaxant administration is to utilize a peripheral nerve stimulator over the course of the ulnar nerve.[37,38,42] The amount of drug needed to produce the desired degree of relaxation and the need for and the amount of additional relaxant required to maintain block can be determined by observation of hand movement. The nature of the block, the adequacy of reversal, and the role of relaxants in postoperative hypoventilation can also be evaluated.

Proper administration of neuromuscular relaxants should allow prompt spontaneous recovery from depolarizing agents, or easy reversal of a nondepolarizing block by anticholinesterases. The existence of a normal tidal volume does *not* represent adequate recovery. The patient *must* have a sufficient respiratory reserve to overcome soft tissue obstruction and be able to breathe deeply and cough. Evaluation of adequate respiratory reserve includes the ability to lift one's head off the bed for a short period of time,[33] the presence of an inspiratory force of at least −20 cm of water exerted against an occluded airway,[89] a vital capacity of greater than 1 liter, and a sustained response to tetanic stimulation of 50 H_z or more.[27]

Prolonged recovery from succinylcholine results from an absolute or relative overdose. Serum cholinesterase hydrolyzes succinylcholine in two phases, transforming succinylcholine into succinylmonocholine and choline, and succinylmonocholine into succinic acid and choline. The hydrolysis is rapid, about 90 per cent occurring in 1 minute. Serum cholinesterase is genetically determined and several abnormal enzyme variants have been identified.[91] Approximately 94 per cent of the population are homozygous for the normal enzyme while about 4 per cent are heterozygous with normal and abnormal types, and individuals homozygous for abnormal enzymes are less than 1 per cent. Data indicate that apnea exists for about 1 hour in abnormal homozygotes following 100 mg succinylcholine, and such individuals receiving 1 mg per kg may require up to 4 hours to achieve a normal vital capacity.[34] Heterozygous individuals will have a slightly prolonged response as well, but the prolongation in succinylcholine effects often remains unidentified during anesthesia. Administration of additional relaxants should not occur until one is satisfied that normal enzymatic destruction of a single dose of succinylcholine has occurred.

With single intravenous injections of 0.5 to 2 mg per kg of succinylcholine, the block is depolarizing in character; doses of 3 to 5 mg

per kg occasionally produce a desensitization block. Intermittent injections and continuous infusion increase the development of desensitization block.[48] Most evidence indicates that the rate of recovery from a block of either mechanism is similar unless an overdose of succinylcholine has been administered and the endplate and plasma are saturated.[12, 28, 48]

During prolonged recovery following succinylcholine, antagonism with an anticholinesterase may be considered. If the desensitization block is diminishing, with relaxant concentrations in plasma and at the endplate falling as evidenced by increasing muscle strength, antagonism can be effective. If a high plasma succinylcholine concentration exists, anticholinesterases will increase the block.[28] Because of the difficulty in assessing plasma levels, anticholinesterases should rarely be used.

Antagonism of nondepolarizing relaxants is routinely effected by the anticholinesterases, neostigmine and pyridostigmine. The point of recovery from neuromuscular block at which reversal is begun is more important than the dose of blocker administered;[19, 40, 41] studies of efficiency of reversal (comparing the ease of reversal of various relaxants or various anticholinesterases) use a certain degree of twitch height as zero time. The greater the spontaneous recovery, the more rapid the return to normal twitch height (Fig. 2). If twitch height spontaneously returns to 25 per cent of control, recovery following neostigmine usually occurs within 10 minutes. Reversal may be prolonged if spontaneous recovery is less.[19, 40, 41]

Neostigmine is the most commonly used anticholinesterase; normally 2.5 mg of neostigmine is administered, mixed with, or preceded by 1 mg of atropine in an adequately oxygenated and ventilated patient. Occasionally up to 5 mg of neostigmine may need to be used if minimal spontaneous recovery has occurred. Experience indicates that more than 5 mg of neostigmine is not of value and may increase block.

Pyridostigmine is also an effective antagonist.[19, 41] It has a lower onset and longer duration of action than neostigmine;[59] there is controversy concerning any difference in the incidence of bradycardia[19, 41] but atropine is commonly used. Pyridostigmine 10 mg is comparable to 2.5 mg of neostigmine. Pyridostigmine may be of importance in situations where the excretion of the relaxant is prolonged or conditions that potentiate nondepolarizers persist.

NEWER AREAS OF UNDERSTANDING

Uptake, Distribution, and Elimination

The uptake and distribution of all relaxants are similar (Fig. 3). Peak muscle concentrations of 25 per cent are seen in 5 to 6 minutes. Throughout and beyond the period the kidney and the liver are eliminating relaxant.[15] Termination of relaxant effects is due to the initial rapid period of distribution and redistribution with tissue binding, and a later, slower period of excretion.

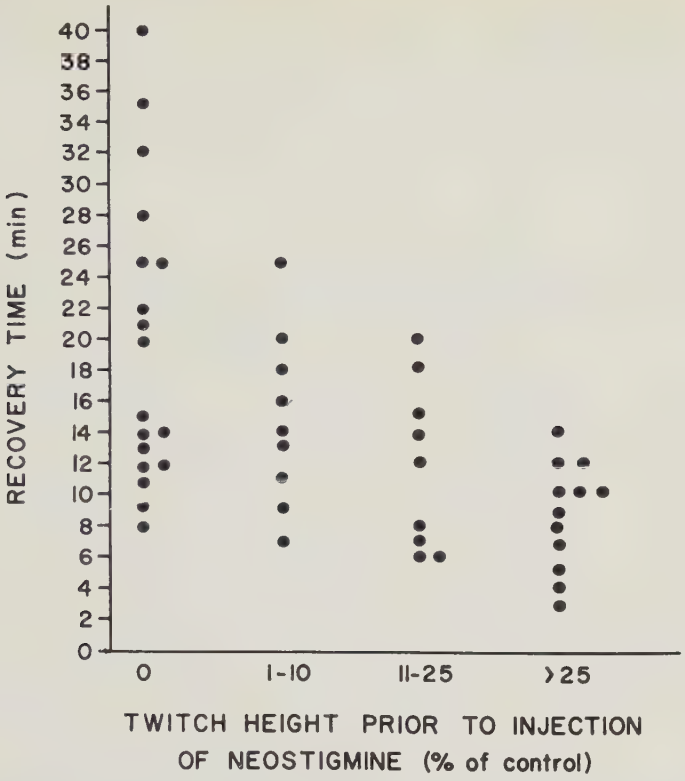

Figure 2. The time required for antagonism of d-tubocurarine by neostigmine. (Reproduced from Katz, R. L.: Neuromuscular effects of d-tubocurarine, edrophonium, and neostigmine in man. Anesthesiology, 28:327–336, 1967. Used with permission.)

Binding of relaxant molecules to plasma protein will modify both the amount available to the nerve-muscle junction as well as the elimination phase. Increased binding of d-tubocurarine with elevated gamma globulins[77] and increased binding of gallamine with elevated albumin have been suggested.[78] There is no abnormal binding of pancuronium.[78]

Renal excretion is an efficient mechanism for elimination of relaxants. The liver represents an alternate excretory pathway for d-tubocurarine with unchanged drug excreted in the bile.[9] A similar situation exists for pancuronium with a small degree of hepatic metabolism as well as hepatic excretion clearing relaxant in the absence of renal function.[1, 53] No alternate pathway exists for gallamine.[18]

D-tubocurarine and pancuronium are commonly used in patients with renal disease.[8, 25, 58] The use of gallamine is hazardous.[8] However, it is prudent to use small amounts of d-tubocurarine and deeper levels of anesthesia because with smaller amounts the duration of action is not affected or only slightly increased. With large or multiple doses, prolonged block may occur.[25, 58]

Few data are available concerning relaxant action in patients with

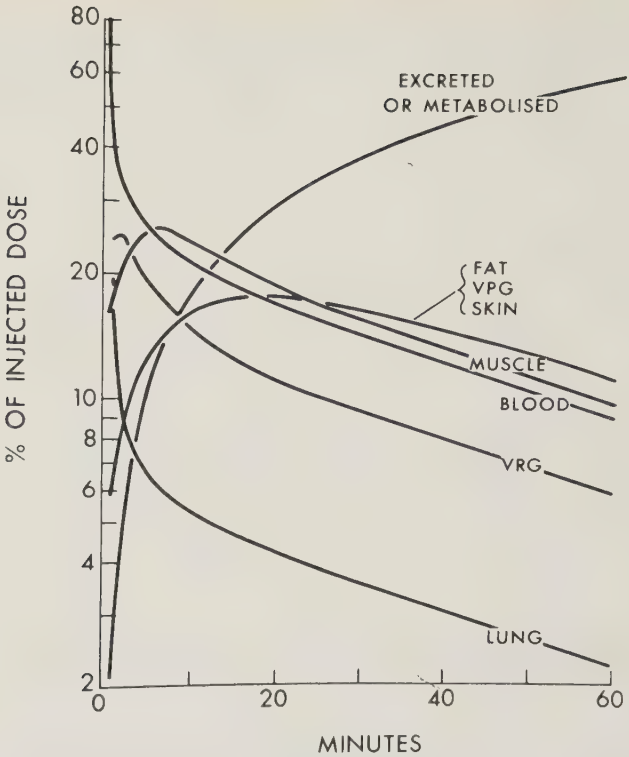

Figure 3. Uptake and distribution of a "typical" relaxant following intravenous injection. (Reproduced from Eger, E., II.: Muscle relaxant uptake and elimination. *In* Anesthetic Uptake and Action. Baltimore, Williams and Wilkins Co., 1974. Used with permission.)

hepatic disease. There is a clinical impression of resistance to d-tubocurarine possibly because of reversed A/G ratios with increased binding to gamma globulin, and the hepatosplenomegaly may offer increased binding sites. Information concerning pancuronium varies based on considerations of the degree of hepatic metabolism and the lack of abnormal binding. Severe hepatic disease will reduce serum cholinesterase, but rarely will the reduction in enzyme amount seriously affect succinylcholine metabolism.[34]

Inhalational Anesthetics

Muscle relaxation achieved with inhalational anesthetics usually results from their action on the central nervous system, producing depression of spinal cord transmission.[67] The anesthetics in clinical concentrations relax skeletal muscle without causing significant neuromuscular block. There are, however, minor actions of inhalational anesthetic at the endplate. Fade is observed at high tetanic rates of stimulus,[56] The neuromuscular refractory period is lengthened,[16] and desensitization of the postjunctional membrane has been observed.[26, 35, 36, 86] High concentrations of diethyl ether[39] and enflurane[57] will decrease

Table 1. *Amount of Pancuronium Needed to Achieve Equal Twitch Depression at .5, 1.0, and 1.5 MAC Isoflurane and Halothane**

	.5	1.0	1.5
Isoflurane per cent	0.5	1.0	1.5
Pancuronium (mg per m^2)	0.6	0.36	0.18
Halothane per cent	0.4	0.8	1.2
Pancuronium (mg per m^2)	0.82	0.49	0.35

*Reproduced from Miller, R. D., et al.: The dependence of pancuronium- and d-tubocurarine-induced neuromuscular blockades on alveolar concentrations of halothane and Forane. Anesthesiology, 37:573–581, 1972. Used with permission.

twitch height. Most importantly, inhalational anesthetics potentiate relaxants. There are two significant aspects (Table 1). One, the greater the depth of general anesthesia, the less relaxant will be needed to achieve a certain depression of twitch height.[62] Second, certain anesthetics produce greater potentiation, so that with certain anesthetics less relaxant is required to achieve a certain reduction in twitch height than with other anesthetics (Table 2).[46, 56, 62, 63] The spectrum of anesthetic agents ranges from N_2O with no potentiation, through halothane, to agents such as diethyl ether, enflurane, and isoflurane which produce major potentiation. This potentiation results from the minor effects of anesthetics at the nerve muscle junction and from increases in muscle blood flow seen with enflurane and isoflurane.[63, 83]

Interaction Between Relaxants

The common clinical practice of blocking the depolarizing effects of succinylcholine with a small dose of nondepolarizers 3 minutes prior to injection of succinylcholine for intubation significantly decreases the duration and intensity of the succinylcholine block and so the dose of succinylcholine must be increased.[13, 61, 84] Gallamine may be a preferable agent, producing adequate suppression of the depolarizing side effects, nondelayed onset of paralysis, and conditions comparable to succinylcholine alone.[13]

Table 2. *Effects of Pancuronium (0.02 mg per kg) and Nitrous Oxide with and without Succinylcholine (1 mg per kg) or Halothane (0.5 to 1 per cent)**

	PANCURONIUM	PANCURONIUM AFTER SUCCINYLCHOLINE	PANCURONIUM WITH HALOTHANE
Magnitude of twitch depression	44 ± 7 per cent (0 to 83)	77 ± 3.6 per cent (55 to 98)	77 ± 4.9 per cent (45 to 98)
Recovery time to 90 per cent of control	16 ± 2.7 min (0 to 34)	26 ± 3 min (16 to 41)	40 ± 3.7 min (23 to 54)

*Modified from work of Katz, R. L.[44]

Using a nondepolarizer following succinylcholine administered for intubation is also common practice. Data available indicate increased duration of block with both greater and lessened intensity (see Table 2).[44, 84]

The use of succinylcholine to aid in abdominal closure during use of a nondepolarizer is not recommended. The depolarizing phase of succinylcholine may antagonize the nondepolarization block producing less relaxation and there will be a need to increase the amount of succinylcholine administered.[84] Overdose of succinylcholine may occur resulting in prolonged recovery. Increasing anesthetic depth or supplementing the nondepolarizer block with small amounts of the same drug at the start of closure is the preferred approach.

Electrolyte Changes and pH

Alterations of electrolyte concentrations and acid-base status have major effects at the nerve-muscle junction. Potassium is the most important electrolyte influencing neuromuscular function. The intracellular to extracellular ratio is important; most situations involving K^+ alterations are chronic and the ratio remains normal. Rapid changes may alter membrane potentials. Hypokalemia potentiates the effects of the nondepolarizers and produces resistance to the depolarizers. However, most situations of K^+ changes are chronic with no effect on relaxant function.[17] A recent evaluation of hyperkalemic patients with renal failure showed no correlation between K^+ levels and large pancuronium doses; with low pancuronium doses, there was some resistance observed.[58] Increase in Mg^{++} and decrease in Ca^{++} diminish the release of ACH at the nerve terminal. Experimentally, high Mg^{++} potentiates nondepolarizers and succinylcholine; there are clinical reports to suggest potentiation of nondepolarizers during administration of $MgSO_4$.[24]

Variation in reports concerning acid-base changes exist because of different experimental preparations, and because of the manner and time course of the pH change in relation to time of relaxant administration. Changes in pH also affect ionization and tissue binding at the receptor and at sites that may remove relaxant from the circulation. Generally whether the pH change is due to respiratory changes or the infusion of acidifying or alkalizing solution, acidosis potentiates d-tubocurarine and antagonizes gallamine and succinylcholine; alkalosis produces the opposite effect.[17, 32, 47] Respiratory acidosis prolongs recovery from a pancuronium block.[68]

Recent data are illustrative of the conflicting data and demonstrate a new experimental approach. Constant infusion rates of d-tubocurarine are established to maintain a 90 per cent reduction in twitch height and respiratory or metabolic changes are then produced. The changing rate of the curare infusion and the ability to reverse the block are evaluated. An HCl infusion increases and $NaHCO_3$ infusion decreases the curare infusion rate necessary to maintain twitch depression. A respiratory alkalosis or metabolic acidosis does not alter the amount of neostigmine required to antagonize the block. A respiratory acidosis or a metabolic alkalosis increases the amount of neostigmine needed for reversal and

in neither case is complete reversal effected until the pH is corrected.[60] The respiratory pH changes have direct clinical application; commonly during reversal patients may develop a respiratory acidosis as one diminishes ventilation to reverse the respiratory alkalosis produced during the anesthetic and as one assesses the adequacy of reversal.

Other Drugs

The cardiac antiarrhythmic agents usually depress membrane conductivity and excitability, and potentiation of relaxants may be seen.[31, 66] Many agents depress serum cholinesterase, especially phospholine eye drops[69] and some antitumor agents.[85] The ester type local anesthetics compete with succinylcholine for serum cholinesterase but the clinical significance of this competition is not clear.

Over 18 antibiotics have been shown experimentally to have neuromuscular blocking properties and ten of these have been associated with muscle weakness in clinical situations.[70] These antibiotics fall into three groups; the mycins, polymyxin and colistin, and the tetracyclines. The major mechanism of block is most clearly established with the mycin group where there is inhibition of the release of ACH prejunctionally.[70]

Clinical reports of prolonged relaxant effects associated with the use of antibiotics involve administration of one or several antibiotics, various routes of antibiotic administration, relaxants, and potentiating inhalational anesthetics.[71] Management suggestions include recognition of potentiating circumstances, limitation of antibiotic dose, and control of the method of administration, especially avoiding washes. Anticholinesterases are not totally effective in antagonism, perhaps because the limited amount of ACH released is insufficient even when its enzymatic destruction is blocked. Experimentally, Ca^{++} and bicarbonate are effective in treatment[74] but Ca^{++} administration is frequently ineffective clinically.

Specific Diseases

Patients with myasthenia gravis show sensitivity to the nondepolarizers.[21, 92] Resistance to the depolarizers has been described,[7, 21, 92] yet succinylcholine is often effective for short periods of relaxation. In clinical practice, relaxants are usually avoided or markedly reduced amounts of nondepolarizers are used and then antagonized. Neuromyopathy marked by muscle weakness and wasting may be seen with malignancy; the myasthenic syndrome is associated with small cell carcinoma of the lung. Sensitivity to both type relaxants is described with this disorder.[92] Patients with lower motor neuron disease may be sensitive to relaxants, especially the nondepolarizers.[73]

Generalized muscle spasms and problems with ventilation frequently follow the use of succinylcholine in patients with various myotonic disorders.[50] Although occasional reports show successful use of depolarizers, muscle relaxation is commonly achieved by nondepolarizing agents. Muscle rigidity following succinylcholine should also alert one to the possibility of malignant hyperpyrexia.

Complications of Depolarization

Succinylcholine produces initial depolarization of muscle as part of the development of the block. The side effects of this depolarization are of considerable interest and are another indication that the action of this relaxant is not benign as its wide use would suggest. Fasciculations increase intra-abdominal and intragastric pressure with danger of regurgitation. Muscle pains occur especially in healthy, young individuals undergoing minor surgical procedures. The incidence of such pain does now always correlate well with the presence or severity of fasciculations,[5, 90] although the association is an appealing explanation for the pain. Intraocular tension is increased by the contraction of the extraocular muscles as well as orbital smooth muscle.[45] Elevation of serum K^+ of up to 0.5 mEq may follow the intravenous use of 60 to 100 mEq of succinylcholine in normal individuals.[4, 52, 88] A similar rise in K^+ in uremic patients is of little hazard expecially if K^+ has been controlled by dialysis.[64] Elevation of serum creatinine phosphokinase[79] and myoglobinuria[2] are occasionally observed.

Individuals with extensive third-degree burns,[82] muscle trauma,[54, 88] and upper and lower motor neuron disease[11, 76, 81] show much larger increases in serum K^+. Increases of 5 mEq with arrhythmias and cardiac arrest have been reported. The danger of hyperkalemia is greatest several weeks to months following burns and trauma and with neurologic disease of recent onset and rapid progression.[10] The mechanism in some disorders is related to increased chemosensitivity of the muscle membrane because of the development of receptor sites in extrajunctional areas.[30, 80]

Approaches to modify or abolish these depolarizing side effects have been many; current clinical practice involves the use of small amounts of a nondepolarizer (d-tubocurarine 3 mg, gallamine 20 mg, or pancuronium 0.5 mg) several minutes prior to succinylcholine. Evidence supports the value of this technique to block fasciculations[13, 61] and the increase in intraocular tension.[65] This approach is not as effective in the prevention of hyperkalemia in susceptible patients, especially in patients with neurologic diseases for whom the danger period is not well defined. The use of adequate amounts of nondepolarizing agents for intubation and relaxation is recommended in such patients.

PANCURONIUM

Pancuronium is a steroid with two attached quaternary ammonium groups but without steroid action.[3] Pancuronium is a nondepolarizing relaxant and the block is readily reversed by anticholinesterases. It is five times more potent than d-tubocurarine, does not produce ganglionic blockade or histamine release, and has no toxicity in doses 25,000 times the blocking dose in cats when ventilation is supported.

Pancuronium is commonly administered in doses related to patient weight. Both the intensity and the duration of the block are modified by the factors previously discussed and by considerations of the degree of

relaxation required. Doses of 0.02 to 0.04 mg per kg produce a minimal to moderate neuromuscular block and 0.06 to 0.1 mg per kg produces profound block (Table 3). The higher dose may also be used to provide conditions for intubation comparable to these produced with succinylcholine.

Early reports suggested the duration of the block is somewhat longer than that produced by d-tubocurarine, but when duration is evaluated by peripheral nerve stimulation, duration is similar with equipotent amounts of d-tubocurarine.[20, 43, 68] There is marked variation in intensity as well (see Table 3). Usually the greater the intensity of the block, the longer the duration. Subsequent equal doses of pancuronium slightly increase the intensity but markedly increase the duration of the block.[43]

While the mechanism of the block and the elimination of pancuronium are similar to d-tubocurarine in most respects, the cardiovascular effects differ. Pancuronium increases heart rate by 16 to 50 per cent, possibly by a vagolytic mechanism. The greatest increase in heart rate is seen in patients with the slowest rates before pancuronium. Systolic blood pressure may increase slightly and cardiac output is increased. Occasionally ventricular extrasystoles or A-V disassociation are seen, usually associated with the use of volatile anesthetic agent such as halothane.[55, 75] Changes in heart rate or blood pressure are not associated with the amount of pancuronium or anesthetic concentration.[55]

Pancuronium represents an important addition to the list of neuromuscular blocking drugs. The advantages of utilizing a long-acting agent that can be reversed at the termination of surgery rather than a continuous infusion of succinylcholine is clear. Of the available nondepolarizing agents, d-tubocurarine produces hypotension by ganglionic blockade and occasionally histamine release.[75] Gallamine, while not producing cardiovascular depression, does not have an alternate excretory pathway besides renal elmination, and there is evidence to suggest that the drug is more difficult to reverse.[57] Pancuronium is increasingly becoming the sole neuromuscular blocker used during an anesthetic. The lack of cardiovascular depression makes it the blocker of choice in the hypovolemic patient, or with vasodilating anesthetics. The depolarizing side effects of succinylcholine can be avoided if intubation is accomplished with the aid of pancuronium.

Table 3. *Effects of Different Pancuronium Doses on Twitch Depression and Recovery**

Dose (mg per kg)	0.02	0.04	0.08
Time from injection to peak effect	332 sec	279 sec	207 sec
Magnitude of twitch depression	44 per cent (0 to 83)	88 per cent (50 to 100)	99.9 per cent
Recovery time to 10 per cent of control	–	14 min (0 to 46)	65 min (33 to 102)
25 per cent of control	–	26 min (0 to 59)	86 min (43 to 133)

*Modified from work of Katz, R. L.[43]

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New Intravenous Anesthetics

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Intravenous anesthetic agents have won widespread acceptance. Physicians promise intravenous anesthesia and patients expect it. Most of the anesthetic drugs administered intravenously have a rapid onset of action. This is a pleasant contrast to the prolonged, struggling ether induction which many patients remember as "anesthesia."

There are many intravenous drugs to choose from. Most are potent and all are deceptively simple to administer. This article will attempt to cover the more common circulatory, respiratory, and neuromuscular actions of the newer intravenous anesthetic agents. The drugs to be discussed include ketamine, newer uses of narcotics, both alone and in neurolept combinations, steroid anesthetics, and other nonbarbiturate anesthetic drugs.

KETAMINE

Ketamine is a derivative of phencyclidine, a drug used extensively in veterinary anesthesia. It was released for general use in the United States in 1971, following over 12,000 administrations in clinical trials. Initial reports suggested that the drug would revolutionize the practice of anesthesia, but as is usually the case, this did not come to pass.

Ketamine is effective when administered either intramuscularly or intravenously. The usual intramuscular dose is about five times as large as the intravenous dose and takes 3 to 4 minutes to become effective, in contrast to a 30 to 60 second onset of action with intravenous use. The duration of action is 5 to 10 minutes after a single intravenous dose and up to 25 minutes after a single intramuscular dose. Repeated doses prolong both anesthesia and recovery time. Overall response to ketamine is similar regardless of route of administration but the intramuscular route may minimize some of the cardiovascular effects.[3]

The term "dissociative anesthesia" was introduced to describe the state of the patient after ketamine. In contrast to the relaxed, obviously unconscious, quiet patient under general anesthesia, dissocia-

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tive anesthesia induced by ketamine is characterized by a cataleptic-like state. Patients often have increased muscle tone, their eyelids remain open—indeed the eyes move as if surveying the surroundings. Perhaps the greatest difference from traditional signs of anesthesia is in patient movement. In the dissociated state, purposeless movements unrelated to surgical stimulation are quite common, and are not controlled by increasing the dose of ketamine. Accepting the sight of an anesthetized patient moving was a problem for many who were accustomed to more traditional anesthesia.

Many of the early papers on ketamine were reports of clinical observation only. Statements like "As airway patency is never a problem, there is no need for an airway cannula," were made.[21] These were followed by clinical observations of potential and actual anesthetic disasters,[26] and finally by studies which attempted to determine the incidence of problems during ketamine anesthesia.[28]

Circulatory Effects

Intravenous ketamine causes increases in heart rate, cardiac index, mean aortic pressure, and mean pulmonary artery pressure.[31] Increased cardiac index cannot be attributed to increased heart rate alone, since administration of ketamine to patients whose heart rates are already raised by pacing causes an increase in cardiac index. This suggests a mechanism involving enhanced myocardial contractility. On the average, no significant change occurs in systemic vascular resistance (SVR) when ketamine is administered, but there is unpredictable individual patient variation.[28]

Ketamine's ability to increase cardiac index and blood pressure has generated enthusiasm for use of the drug in patients who are hypotensive for a variety of reasons. The individual variability in SVR response, however, points out a potential danger. A slight decrease in systemic vascular resistance could unmask a compensated hypovolemic state and thus create profound hypotension. Caution must be exercised also in the use of ketamine in hypertensive patients, where further increase in arterial blood pressure or in myocardial work would be undesirable.

Respiratory Effects

Ketamine commonly provides a clear, unobstructed airway, protected at least in part by normal reflexes.[4] Too rapid intravenous administration can, however, cause soft tissue obstruction of the airway, severe respiratory depression, or even apnea. Ketamine had been suggested as the sole anesthetic agent for the patient with a full stomach, but subsequent studies have shown that significant aspiration can occur despite the apparent preservation of airway reflexes.[19, 29]

Active or only partially depressed airway reflexes pose a problem during surgery on the pharynx or larynx. Surgical stimulation of these areas will almost predictably result in coughing or laryngospasm. For these reasons, among others, ketamine is not recommended for oral, pharyngeal, or laryngeal operations.

Sussman[28] reported that 10 per cent of all ketamine anesthetics in patients over 30 years of age were unsatisfactory because of airway difficulties (laryngospasm, coughing, or upper airway obstruction). This ob-

viously represents a serious problem and underscores the necessity for administration of ketamine only by personnel skilled in airway management and ventilation.

Other Effects

Ketamine has been shown[33] to increase intracranial pressure. Many authors feel the drug should be used with great caution, if at all, in patients with signs or symptoms of increased intracranial pressure.[3, 12, 33]

Since the dissociated state induced by ketamine is commonly accompanied by spontaneous movements and increased muscle tone, physical restraint or muscle relaxant drugs may be necessary. Increased muscle tone most commonly presents as difficulty in positioning the patient. Firm, constant pressure will usually overcome such rigidity.

Perhaps the greatest obstacle to widespread acceptance of ketamine, especially in adults, has been the occurrence of hallucinations and emergence delirium. A vivid description of a ketamine experience was published in 1973.[17] Sussman[28] reported occurrence of emergence phenomena (nightmares, delirium, hallucinations) in 24 per cent of patients over 15 years of age. While some patients report pleasant dreams (and can report their experience in great detail), others have obviously had a terrifying experience, and request that they not receive ketamine for subsequent anesthetics. Over 40 per cent of the patients in Hervey and Husted's[14] group made such a request. Prevention and control of these psychic side effects has not been totally successful. Tranquilizers in the pre- and postanesthetic period and postoperative narcotic or barbiturate have all been suggested,[3] but none has been uniformly satisfactory. Unpleasant psychic side effects are less common in children, and in some anesthetic practices, ketamine is restricted to pediatric use.

Current Status

Following the initial enthusiasm and subsequent backlash, ketamine is finding its place in anesthetic practice. It is an excellent drug for many pediatric diagnostic and minor therapeutic procedures. Patients requiring repeated anesthetics, e.g., burn dressing changes, may be cared for with minimal disruption of nutrition. Ketamine has gained some popularity as an induction agent, since a single dose given either intravenously or intramuscularly can render a patient amnesic. The hypotensive patient may benefit from ketamine, but an even lower blood pressure is also a possibility.

Ketamine does not provide muscular relaxation and appears to block visceral pain inadequately.[29] The reactivity of pharyngeal and laryngeal reflexes precludes ketamine anesthesia for most operations within the oropharynx. Increased systemic blood pressure and increased intracranial pressure can be relative contraindications to use of the drug.

NEWER USES OF NARCOTICS

Narcotic analgesic drugs have recently assumed a new role as primary anesthetic agents for general anesthesia. The use of a narcotic drug as the primary anesthetic agent was described by Bailey[1] in 1958.

In 1969, Lowenstein et al.[23] reported their experience with morphine-oxygen anesthesia in patients with cardiac disease. Morphine was found to be a strikingly benign drug—actually increasing cardiac index.

The findings reported by Lowenstein triggered a wave of popularity for morphine anesthesia, especially for cardiac surgery. It was felt that morphine in doses from 0.5 to 3 mg per kg had little effect on myocardial contractility, in contrast to most of the inhalation anesthetic agents, which are known myocardial depressants. As experience with morphine anesthesia grew, the technique came to be utilized outside cardiac anesthesia for all types of critically ill patients.

Circulatory Effects

In a study of healthy volunteers,[32] consciousness was not lost even when the morphine dose reached 2 mg per kg. Cardiac index and stroke volume index increased with morphine-oxygen "anesthesia," but total peripheral resistance decreased, creating a situation in which the mean arterial blood pressure did not change. The addition of nitrous oxide to a morphine-oxygen "anesthetic" caused the healthy volunteer subjects to lose consciousness, and the heart rate, cardiac index, and stroke volume index to fall. Mean arterial blood pressure remained unchanged, however, because total peripheral resistance increased.

A study[6] of morphine in patients undergoing cardiac valve surgery found an incidence of clinically significant hypotension. Morphine can lower blood pressure through several mechanisms, including: (1) decreased consciousness and physical activity, (2) decreased respiratory drive with hypoxia and hypercapnia, (3) histamine release, and (4) centrally mediated peripheral vasodilatation.

These factors combine to increase the capacity of the peripheral vascular system, decreasing the amount of blood returned to the heart, thus lowering cardiac output and systemic blood pressure. Such hypotension is often transient, and may usually be treated by maneuvers which increase venous return to the heart (head down tilt, increased intravenous fluids, peripheral vasoconstrictor drugs). Occasionally, direct myocardial stimulants (epinephrine, isoproterenol) are required.

Severe hypertension may also occur during morphine anesthesia.[6] It appears to be a vascular phenomenon, rather than a response to light anesthesia. Increasing the morphine dose has no effect, but use of a rapid-acting peripheral vasodilating drug will return arterial blood pressure to acceptable levels. The mechanism of morphine hypertension is not clearly understood, but may be related to increased alpha-adrenergic activity.

Respiratory Effects

Narcotics depress respiration. They act on brainstem respiratory centers to decrease responsiveness to elevated P_aCO_2.[16] Investigators[20] have related tales of experimental subjects who had received morphine doses in the range of 2 mg per kg. The subjects were awake and relatively alert—but had to be reminded to breathe! The use of narcotic anesthesia, particularly morphine, presupposes the ability to ventilate the patient mechanically for at least 24 hours. Depression of the drive to

breathe has been shown to be present the day following morphine anesthesia.[2]

The availability of naloxone, a narcotic antagonist which has no intrinsic depressant properties, prompted attempts at "turning the morphine anesthesia off" after surgery was completed. Unfortunately, the duration of action of the antagonist is much shorter than that of morphine, so that repeated doses of naloxone are required,[18] and *constant* observation of the patient is *mandatory*. The safer and more practical course is mechanical support of ventilation until the narcotic's effects have dissipated.

Other Effects

Rapid intravenous administration of narcotic analgesic drugs may result in spasm of the voluntary muscles of the chest wall. When this situation arises, a small dose of muscle relaxant is necessary to permit the anesthesiologist to ventilate the patient's lungs. If, however, the patient has not completely lost consciousness, the anesthesiologist can direct the patient to initiate inhalation and can then gently assist the patient's respiratory effort.

Morphine anesthesia must be supplemented with muscle relaxants where operating conditions require skeletal muscle relaxation.

Current Status

The increasing frequency of coronary artery surgery is forcing a reevaluation of morphine anesthesia.[22] Normal blood pressure and increased cardiac output may be produced at the expense of increased myocardial oxygen demand, which is probably not desirable in a patient whose cardiac oxygen delivery system is compromised by coronary occlusive disease. No single agent stands out as the obvious choice for these patients at this time.

NEUROLEPT ANALGESIA AND ANESTHESIA

The prefix "neurolept" has been adopted to refer to the state produced by the combination of a major tranquilizer and a narcotic. Neuroleptanalgesia is characterized by tranquilization and intense analgesia with minimal hypnosis. Many physicians and patients would view the state as ideal sedation, with somnolence but retained consciousness, psychologic detachment from the environment, analgesia, and some amnesia.

Many drug combinations have been used to achieve neuroleptanalgesia. The effectiveness of any combination probably depends at least as much on the skill and judgment of the prescriber as it does on the choice of drugs. Innovar is a commonly used neurolept combination.• Droperidol (a long-acting butyrophenone tranquilizer) and fentanyl (a short-acting synthetic narcotic) are combined in a 50:1 ratio.

The "neurolept" prefix is also added to -anesthesia, signifying the addition of hypnosis to the other qualities characterizing neuroleptanalgesia. This is most commonly accomplished by the inhalation of ni-

trous oxide in oxygen during and after administration of the neurolept combination.

Circulatory Effects

Droperidol usually causes a slight decrease in blood pressure in the supine patient. The mechanism is believed to be weak alpha blockade with resultant peripheral vasodilatation. Some authors feel that droperidol protects against epinephrine-induced cardiac arrhythmias.[25] Fentanyl is a narcotic and shares the potential hypotensive properties of that class of drugs. Increased parasympathomimetic activity from the narcotic may cause a bradycardia which can be prevented or treated with atropine.

Respiratory Effects

Fentanyl is a potent narcotic which depresses respiration just as does morphine. With equianalgesic doses of either drug, respiratory depression is equally severe, but of shorter duration with fentanyl. Droperidol potentiates the effects of any depressant drug and prolongs narcotic-induced respiratory depression. Subsequent doses of narcotic, barbiturate, or any other analgesic, sedative, or hypnotic must be carefully titrated to the patient's need and ability to tolerate.

Other Effects

Neuroleptanesthesia provides no direct muscle relaxation. If the operation requires paralysis, muscle relaxants must be used. Occasionally tranquilizers used in neurolept combinations may cause extrapyramidal reactions. These can be treated with benztropine or atropine.

Emergence from neuroleptanesthesia is usually smooth and rapid—consciousness returns within minutes of the cessation of N_2O. Postoperative nausea and vomiting are reduced because of the antiemetic properties of droperidol.[15]

Current Status

Innovar has become widely used both for sedation and for neuroleptanesthesia. It is a potent premedicant, producing a tranquil, cooperative patient. It is a useful adjunct to hypnoidal induction techniques.

Neuroleptanesthesia offers a potent, nonexplosive, nonhepatotoxic technique for general anesthesia. The drugs employed are powerful, and severe circulatory or respiratory depression can result. Emphasis must again be placed on the individualization of dosage, and the undivided attention which the anesthesiologist owes his patient.

OTHER NONBARBITURATE ANESTHETICS

Diazepam

Diazepam (Valium) is not an anesthetic drug. It is a tranquilizer, a benzodiazepine derivative, often used for sedation and to alleviate anxiety. Intravenous doses may be used to provide amnesia for short procedures such as gastroscopy or cardioversion.

Diazepam's ability to produce sedation and amnesia have led to its use as an "induction" agent for general anesthesia. Sedated by intravenous diazepam, the patient readily accepts inhalation anesthesia.

In a study of 15 patients given 5 to 10 mg of diazepam intravenously during cardiac catheterization, Dalen demonstrated minimal cardiovascular changes. Mean cardiac index remained unchanged, although arterial blood pressure decreased slightly. These changes appear to be of little clinical significance.

Diazepam in small (5 to 10 mg) intravenous doses produces respiratory depression.[8] Most patients given diazepam exhibit a slightly elevated P_aCO_2 and a decrease in the slope of the CO_2 response curve, but are capable of adequate respiratory exchange. The respiratory response of a given patient to intravenous diazepam is unpredictable.[5]

As with any other drug capable of causing unconsciousness, soft tissue obstruction of the airway may occur following administration of diazepam. The ability to deal with this problem is incumbent upon the person utilizing intravenous diazepam.

The manufacturer suggests slow injection directly into a large vein. The solution for injection is irritating and can cause pain and inflammation along the course of the vein.

Steroid Anesthetics

The anesthetic properties of steroids were reported in 1941[27] but the problems of solubility, side effects, and potency have plagued investigators in this area. Alphadione (Althesin) is a combination of two steroids in a solubilizing agent. Initial clinical reports describe a drug which produces unconsciousness rapidly after intravenous injection.[9] Circulatory depression is usually mild, related primarily to peripheral vasodilatation.[11] Transient depression of respiration occurs with tidal volume and minute ventilation regaining preanesthetic levels within minutes.[30] Emergence is reported to be pleasant, even euphoric at times. Duration of anesthesia is dose-related.

Alphadione is not an analgesic. It is, therefore, not considered an agent for maintenance of anesthesia. Involuntary muscle twitching and hiccuping are common side effects. The solubilizing agent, Cremophor EL, has been implicated in some of the more serious complications seen with alphadione including hypotension, anaphylactoid reaction with bronchospasm, and severe cardiorespiratory collapse. Hormonal effects are thought to be unlikely in usual clinical use, and alphadione appears to be different enough chemically to avoid the thermogenic effects which have eliminated many other steroids from clinical consideration.[13]

Alphadione is currently undergoing clinical study in many parts of the world. It is not available for general clinical use in the United States.

Propranidid

Propranidid is an organic ester, derived from oil of cloves. It has a rapid onset and a short duration of action, described as similar to thiopental. Recovery is free from the "hangover" associated with barbiturates. Blood pressure falls in response to intravenous propranidid, and respira-

tion is first stimulated, then transiently depressed.[7] The problems with blood pressure have been serious enough to raise the question of the acceptability of the drug. Except for the clear headed recovery, propranidid seems to offer no great advantage over the barbiturate induction agents. Propranidid is not available in the United States.

Etomidate

Still another approach to intravenous anesthesia is represented by Etomidate, a water-soluble compound currently undergoing clinical trials in the United States and abroad. Loss of consciousness is rapid (about 30 seconds) and respiratory depression is transient. Blood pressure generally remains stable, but one study demonstrated a clinically important incidence of hypotension.[24] Transient involuntary muscular activity is common but apparently is not a problem. Etomidate is said to be the only intravenous hypnotic drug which does not cause histamine release.[10] The clinical implications of this finding remain to be tested, but such a drug could be quite valuable for anesthetizing asthmatics.

CONCLUSIONS

The search for the perfect anesthetic continues. Both anesthesiologists and the laity will continue to support the convenience and speed of the intravenous route of drug administration. Currently thiopental is the standard to which new drugs are compared. It seems likely to remain so for the immediate future.

The perfect intravenous anesthetic will produce profound analgesia as well as loss of consciousness within seconds after injection. It will be nonirritating, water-soluble, and cause neither stimulation nor depression of the cardiovascular and respiratory systems. Emergence will be smooth and rapid with no hangover. Such a drug will probably never exist.

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Regional Anesthesia

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Although peripheral nerve blocks, when properly administered, may provide the safest form of anesthesia for many surgical procedures, they are not currently widely used for several reasons. From the surgeon's point of view, the time required to perform most nerve blocks, and the delay until anesthesia is complete (if it is), are too long. Multiple injections are usually required and thus the surgical schedule is "needlessly" delayed. In addition, the incidence of unsatisfactory anesthesia is high, often requiring the administration of supplemental inhalation or intravenous anesthesia. From the point of view of the anesthesiologist, particularly if he had little opportunity during his training to develop expertise with this form of anesthesia, fear of failure may be an important deterrent. This is especially so if the block must be carried out in the presence of an eager, inquisitive resident or an impatient, pacing surgeon. Perhaps equally dissuasive is the fear of complications such as postanesthetic neuropathy, which is felt to occur as a fairly frequent sequela to block anesthesia (particularly in the hands of the inexperienced), and which enhances the chances of litigation. And last, and certainly not least, from the patient's point of view, multiple injections and paresthesias are objectionable, and the prospect of being "wide awake" during surgery is frightening to some.

It is critical, if regional anesthesia is to be satisfactory to the patient, for the surgeon and anesthetist to agree *in advance* that this is the best form of anesthesia for him, so that there is no apparent disagreement when each of them discusses the matter with the patient. His apprehension about being awake during the administration of a block and the performance of surgery, both of which he fears might be painful, may be alleviated (1) by appropriate counseling by the surgeon *prior* to the patient's admission on the advantages of this form of anesthesia; (2) by the supportive re-enforcement of the anesthesiologist on the preoperative visit, when the details of the particular technique can be explained, including the drugs which will be utilized to allay apprehension, minimize discomfort, and produce a light sleep; and (3) by the judicious choice of adjunctive preoperative and intraoperative medications to

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provide tranquility, amnesia, and sleep. If all of these practices are carried out, it is the rare patient who will not "*prefer*" regional anesthesia.

It occurred to the author a little over a decade ago that if all regional techniques could be carried out by a single injection, as is done with spinal and epidural anesthesia, then virtually all of the objections of the surgeons and anesthetists would be overcome. By its very simplicity, a single injection technique would minimize the degree of skill and experience required to perform a successful block, would markedly reduce the time in its performance, and would certainly enhance its safety, since such complications as intravascular injection and postinjection neuropathy are known to be a function of the number of injections.[5, 11] Obviously, it is also preferable from the patient's point of view if one "needle stick" can replace many. Therefore, over the past decade we have attempted to develop techniques where a single thrust of the needle identifies a particular fascial plane within which the appropriate plexus lies rather than a particular nerve. Thus injection within such an "interfascial compartment" and the use of an appropriate volume allows the anesthetic solution rather than the needle "to seek out the nerves of the plexus," just as is done when one utilizes spinal or peridural anesthesia. Such an approach has been extremely successful in simplifying block anesthesia for surgery on all four extremities, and comprises the substance of this article.

PERIVASCULAR TECHNIQUES OF BRACHIAL PLEXUS BLOCK

Anatomic Principles

The single injection techniques developed to provide anesthesia for the upper extremity have as their basis the fact that the brachial plexus is enveloped by an extension of the prevertebral fascia from the cervical vertebrae to the distal axilla. The anterior scalene muscle arises from the anterior tubercles of the transverse processes of the third, fourth, fifth, and sixth cervical vertebrae, and inserts on the scalene tubercle of the first rib, separating the subclavian vein from the subclavian artery, which lies posterior to this insertion. The middle scalene muscle arises from the posterior tubercles of the transverse processes of the lower six cervical vertebrae. Its insertion is separated from that of the anterior scalene by the subclavian groove through which the artery passes.

The roots of the nerves comprising the brachial (and cervical) plexus travel along the groove between the anterior and posterior tubercles of the transverse processes of the cervical vertebrae, emerging from the "gutters" of the cervical transverse processes. They descend toward the first rib between the two walls of fascia covering the anterior and middle scalene, i.e., they enter the interscalene space. As the roots pass down through this space they converge to form the trunks of the brachial plexus, which together with the subclavian artery invaginate the scalene fascia to form a subclavian perivascular sheath, which in turn becomes the axillary sheath as it passes under the clavicle.

The important concept is that of a continuous fascia-enclosed space extending from the cervical transverse processes to several centimeters beyond the axilla, or from the roots of the brachial plexus to the great nerves of the upper arm. The existence of such a continuous perineural (and perivascular) space renders brachial plexus block very simple. Just as with peridural techniques, the space described may be entered at any level, and the volume of anesthetic injected at that level will determine the extent of anesthesia. Thus, the technique to be used in any given case should be determined on the basis of the surgical site, the required level of anesthesia, and the physical status and habitus of the patient, not on the basis of the anesthetist's bias or training.

Axillary Perivascular Technique of Brachial Plexus Block

The traditional practice in performing an axillary block of making two injections, one superior and one inferior to the axillary artery, seems no more logical to the author than making anterior and posterior injections in the epidural space.[18] Accordingly, we and others have simplified the technique by making a single injection of solution into the perivascular space without decreasing the high percentage of successful blocks achieved with the two-injection technique. In addition we place the needle as high in the axilla as possible to reduce the amount of solu-

Figure 1. Axillary perivascular brachial plexus block (author's technique). A single injection is made superiorly tangential to the arterial pulse. The palpating finger collapses the vein and rolls it inferiorly, minimizing the possibility of venipuncture.

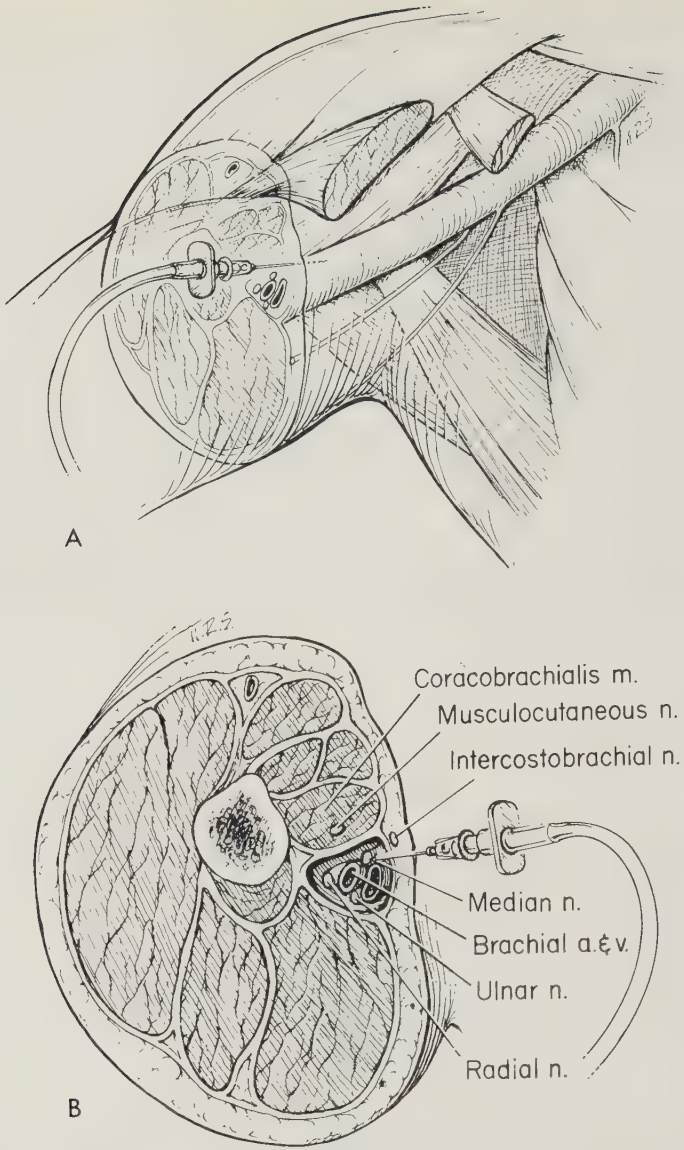


Figure 2. *A*, Frontal view of needle properly placed for axillary perivascular block. Note that direction of needle and position of needle tip promote cephalad spread of injected solution. *B*, Cross-section of needle properly placed for axillary perivascular block. Note that tip of needle lies superiorly tangential to the artery and vein.

tion necessary to reach the musculocutaneous and axillary nerves, which leave the sheath at a very high level. The patient is placed in the supine position with the arm abducted 90 degrees and the forearm flexed and externally rotated so that the dorsum of the hand lies on the table next to the patient's head (Fig. 1). The axillary artery is palpated

and followed proximally as far as possible to the point where it disappears under the pectoralis major. At this point, with the index finger directly over the pulse, a 1½ inch 21 gauge needle is inserted just above the finger tip toward the apex of the axilla such that it will form a 10 to 20 degree angle with the artery as it is advanced. The artery is thus approached gradually until the definite "click" caused by the penetration of the axillary sheath is encountered. The tip of the needle now lies superiorly tangential to the arterial wall 1 to 1½ inches above the most proximal point of palpable pulsation (Fig. 2). If properly placed, the needle will clearly pulsate. Following aspiration, 20 to 40 ml (depending on patient's size, sex, and age and the level of anesthesia desired) of anesthetic is injected slowly with repeated aspiration for blood intermittently during the injection. Volume-anesthesia relationships with this technique have been worked out by taking x-rays after injecting radiopaque dye into the axillary perivascular space. An injection of 20 ml is insufficient to *consistently* assure anesthesia of the musculocutaneous and axillary nerves, so if anesthesia in their distribution and/or relaxation of the powerful flexors of the forearm is essential, 30 or 40 ml is necessary depending on the size of the patient (Fig. 3). Two to three ml of anesthetic is retained in the syringe and, as the needle is being withdrawn, this is deposited subcutaneously over the artery (Fig. 4*A*). This effectively blocks the intercostobrachial nerve which runs just superficial to the sheath to innervate the upper inner aspect of the arm.

If it is essential to use a lower volume of anesthetic because of a patient's debilitated condition, the musculocutaneous nerve can be blocked separately after blocking the intercostobrachial nerve *without* a separate skin puncture by reinserting the needle superior to the entire neurovascular bundle and injecting 5 ml into the substance of the coracobrachialis muscle (Fig. 4*B*). It is not necessary to obtain parasthesias of this nerve unless the onset of anesthesia must be immediate.

As with the other techniques, the axillary perivascular technique has certain distinct advantages and disadvantages. Inadvertent block of the phrenic, vagus, and recurrent laryngeal nerves and the stellate ganglion is virtually impossible with this technique, as is pneumothorax and subarachnoid or epidural injection. These features also make it possible to do bilateral brachial block without fear of respiratory embarrassment. An additional feature which is desirable from the patient's point of view is the fact that it is not necessary to elicit paresthesias. Among the disadvantages is the fact that this technique cannot be used when the patient is unable to abduct the arm to expose the axilla. In addition the axillary perivascular technique requires larger volumes of anesthetic than supraclavicular techniques, though the necessary volume can be minimized somewhat by blocking the musculocutaneous nerve separately as described above. Puncture of the artery or vein is possible, and though vigorous digital massage usually avoids hematoma formation, if it does occur, it is usually of no clinical significance. The chance of intravenous injection is minimized in the technique described by compressing the vein and displacing it slightly downward with the index finger, by using a *single* injection *superior* to the vessels, and by repeatedly aspirating before and during the injection. Intravenous injec-

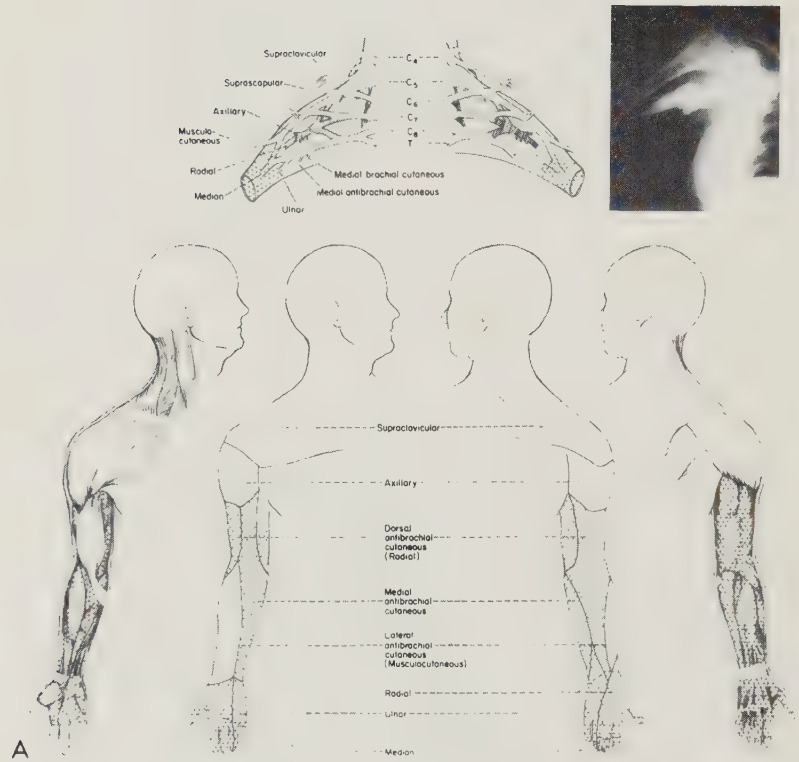


Figure 3. *A*, Volume-anesthesia relationships after injection of 20 ml of solution into axillary sheath. Note the absence of sensory and motor block in distribution of musculocutaneous nerve.

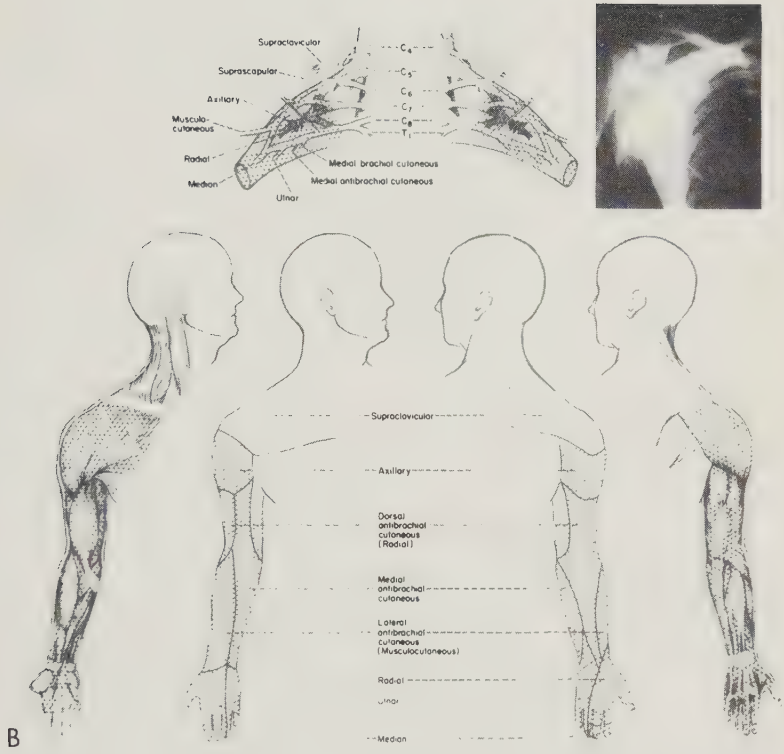


Figure 3 *Continued.* *B,* Volume-anesthesia relationships after injection of 40 ml of solution into axillary sheath. All elements of brachial plexus are blocked by this volume.

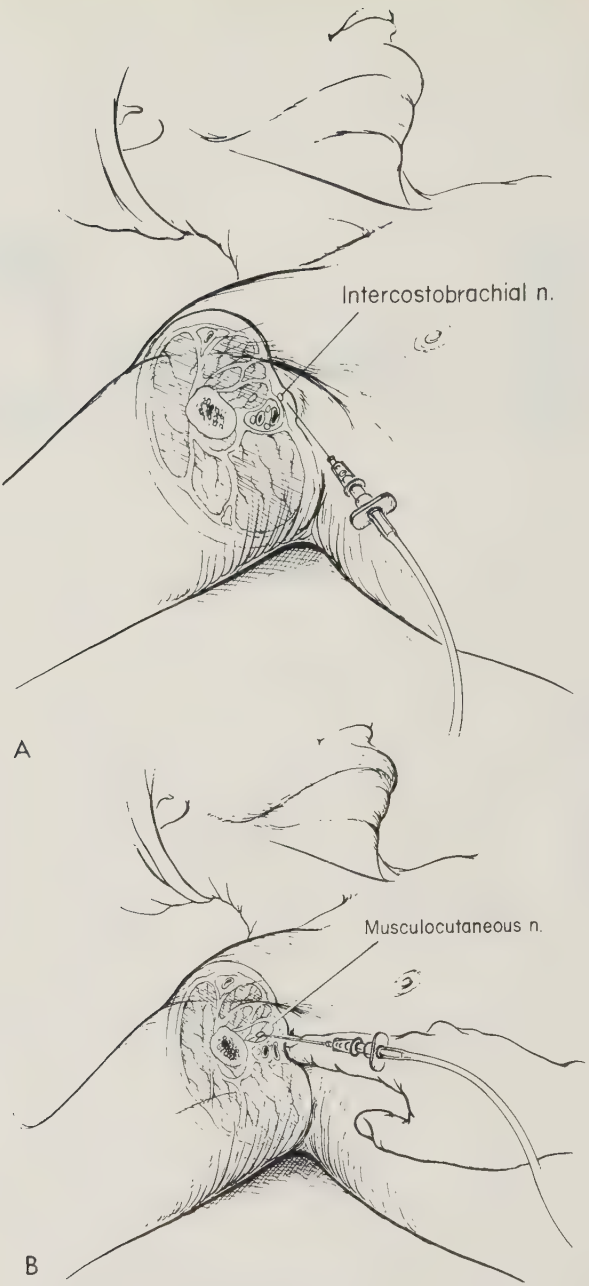


Figure 4. *A*, The intercostobrachial nerve is blocked by depositing 2 ml of local anesthesia subcutaneously superficial to the arterial pulse.

B, The musculocutaneous nerve may be blocked separately (to minimize the volume required) by injecting into the substance of the coracobrachialis muscle.

tion, should it occur, will result in excitement garrulousness, and possibly convulsions, depending on the amount of the injection that entered the vein. Such a complication should be treated with oxygen and diazepam to prevent or terminate a convulsion. The use of barbiturates or other related drugs should be avoided for the sequelae to intravenous injection are usually self-limited and of short duration. Intra-arterial injection, although theoretically possible, has never been experienced by us or described in the literature.

The axillary perivascular technique is contraindicated when there is active infection or malignancy in the involved extremities, because of the lymphadenopathy in such cases. Although this is an easy technique to learn, it is very difficult to use in the very obese or any other situation where the axillary artery cannot be precisely located.

Subclavian Perivascular Technique of Brachial Plexus Block

There are several features of traditional supraclavicular brachial block techniques that can be criticized on an anatomic basis alone.[19] First, the site of needle insertion is usually made 1 cm above the midpoint of the clavicle, and it has been shown by actual dissection that this point frequently does *not* lie over the first rib as described. Since the latter is supposed to act as a "backstop" to protect the cupola of the lung, it is remarkable that the incidence of pneumothorax is not even higher than the 0.5 to 6 per cent reported in the literature.[12] Secondly, the direction of needle insertion is described as mesiad, caudad, and dorsad, and consideration of the anatomy of the "brachial plexus" sheath makes this illogical. Since the subclavian perivascular space is bounded by the anterior and middle scalene muscles, it is deep and very narrow in its anterior-posterior dimension. Thus the direction of the needle insertion advocated in the classic technique results in the needle *crossing* the space in its narrowest diameter. Even the slightest movement during injection may cause the needle to leave the space, and with multiple injections this possibility is increased. Thirdly, the needle is "walked along the rib" to obtain consecutive parasthesias of various distributions with an injection of anesthetic being made each time a paresthesia is elicited. This is illogical since the trunks lie one atop the other vertically as they cross the first rib and not one behind the other horizontally as depicted in so many texts. As a result, the classic technique results in the use of large volumes of anesthetic solution, of which only a small amount may actually be within the sheath, while the remainder may be at the phrenic, vagus, or recurrent laryngeal nerves, or worse still, in the cupola of the lung. It is no wonder that Adriani wrote, "when (we) use the supraclavicular route, (we) do so with a certain amount of fear and trepidation."

Applying the perivascular technique to the supraclavicular approach obviates the undesirable features of the classic technique, which is modified as follows. The patient is in the dorsal recumbent position with the head turned somewhat to the side opposite that to be injected. He reaches for his knee (to lower the clavicle) and then relaxes the arm and shoulder completely. He is then asked to elevate his head slightly to bring the clavicular head of the sternocleidomastoid muscle

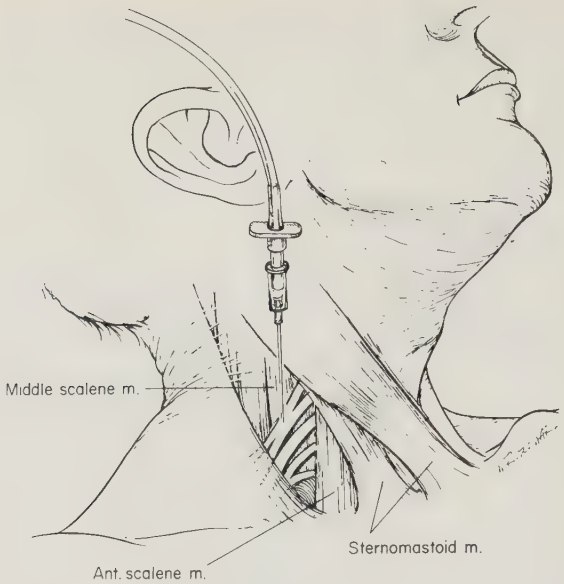


Figure 5. The subclavian perivascular technique of brachial plexus block.

into prominence. Beginning at the lateral border of this muscle, the index finger is rolled laterally across the bell of the anterior scalene muscle until the interscalene groove is palpated. The finger is moved inferiorly along the groove until the pulse of the subclavian artery is palpated as it emerges from between the scalene muscles. With the finger still on the artery, a 1½ inch 21 gauge needle is inserted above this point in a direction that is directly caudad but *not* mesiad or dorsad (Fig. 5). The direction of insertion is such that the needle will be dorsally tangential to the subclavian artery in the longest dimension of the interscalene space where the depth allows considerably more movement of the needle without its leaving the space (Fig. 6). If the needle is advanced slowly, the click of the needle penetrating the sheath may be perceived, though it is less pronounced than that of the axillary sheath; and a short distance beyond, a single paresthesia to the hand confirms the fact that the needle is definitely in the perivascular space. At this point, after appropriate aspiration, the entire anesthetic injection is made. Usually, at the beginning of the injection, "pressure paresthesia," similar to that seen when anesthetic solution is injected rapidly into the caudal canal, offers further evidence that the needle is properly placed.

The relationship between volume injected and extent of anesthesia has been demonstrated by injecting radiopaque dye into the sheath; and it has been shown that 20 ml of dye injected into the subclavian perivascular space extends from the level of the roots to the cords of the brachial plexus. Hence, the anesthesia provided by this volume of anesthetic in the subclavian perivascular space results in motor and sensory loss almost identical to that produced by 40 ml in the axillary perivascular space (Fig. 7*A*). The only way to differentiate which technique has

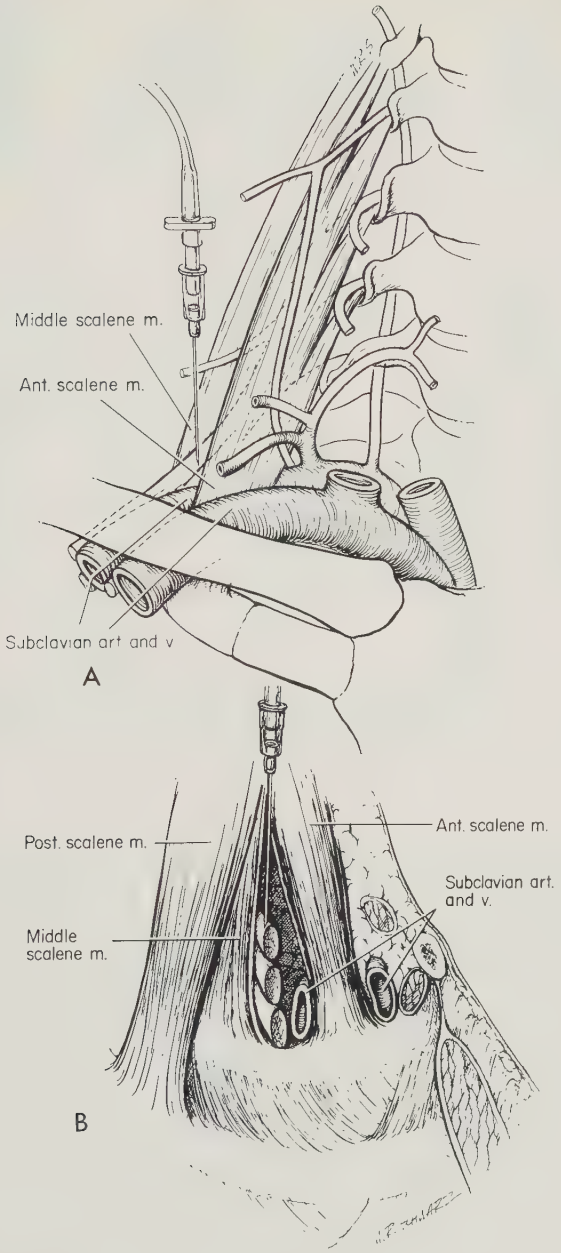


Figure 6. *A*, Frontal section of needle properly placed for subclavian perivascular block. Note direct caudad direction.

B, Sagittal section to show that the caudally directed needle lies in the longest axis of the subclavian perivascular space.

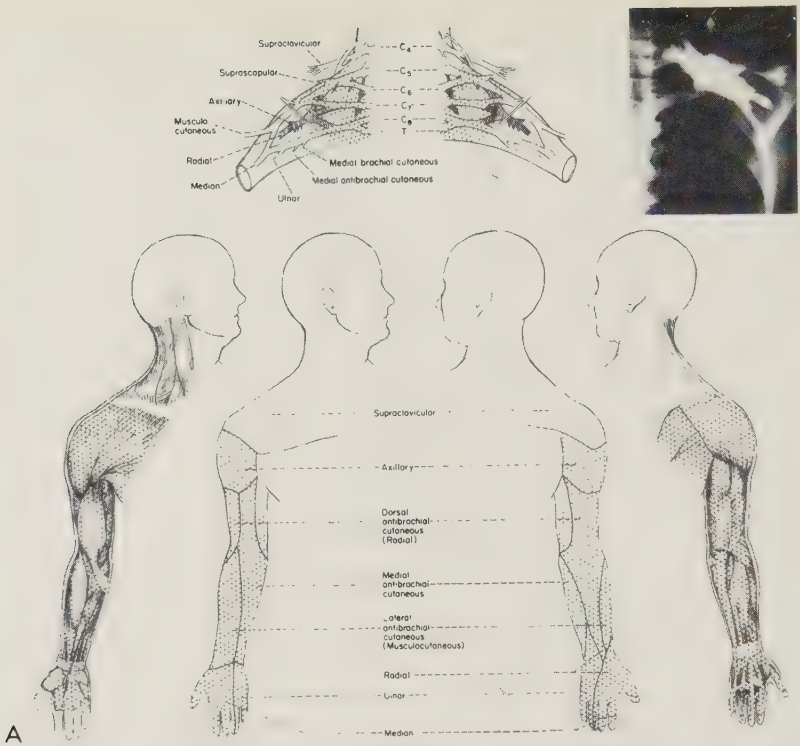


Figure 7. *A*, Volume-anesthesia relationships after injection of 20 ml of solution into the subclavian perivascular space. Note that anesthesia is identical to that achieved with 40 ml injected into the axillary perivascular space.

been used is to note the onset of motor block. The patient who has received the subclavian perivascular block will be unable to elevate the arm shortly after the injection as the flexors and abductors of the arm are the first to be blocked. The patient who has received the axillary perivascular block will be able to elevate the arm, but as it reaches the vertical position, the hand will fall as the extensors of the forearm are the first to be blocked with this technique. An x-ray taken after a 40 ml injection of dye into the subclavian perivascular space shows spread to a higher (and lower) level so that when this volume of anesthetic is used, anesthesia of the cervical as well as brachial plexus results (Fig. 7*B*). Of course, the intercostobrachial nerve must be blocked separately if a tourniquet is to be used, just as with other techniques (see Fig. 4*A*).

The direction of needle insertion, the use of a short needle, and the use of a single injection tend not only to improve the incidence of satisfactory results, but also to minimize the possibility of pneumothorax. Since the direction of needle insertion is parallel to the borders of the scalene muscles and since these muscles insert on the first rib, the position of the rib and vessel is located more precisely with this technique than with any other, although with this technique, in the vast majority of cases, paresthesias are obtained *before* the rib has been contacted. Its

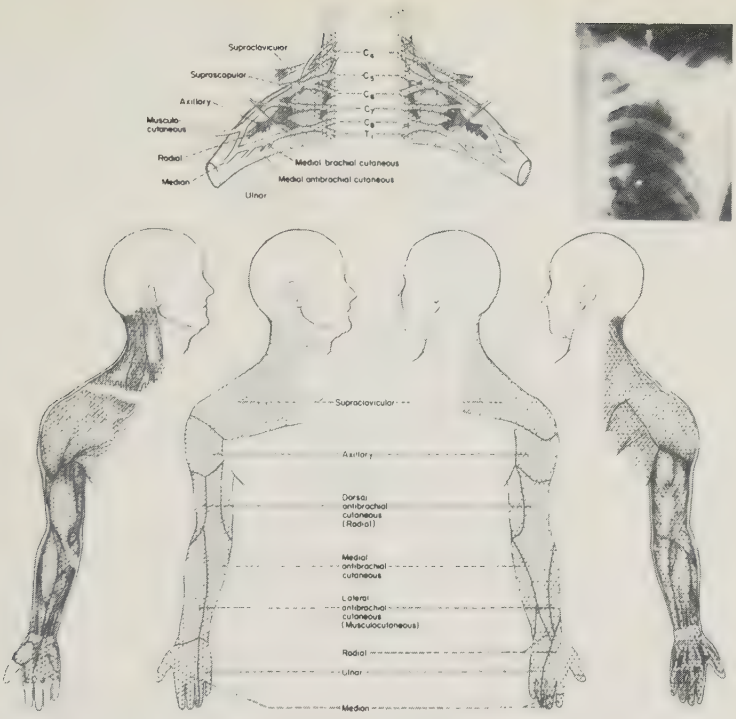


Figure 7 *Continued.* *B,* Volume-anesthesia relationships after injection of 40 ml of solution into the subclavian perivascular space. Arrow denotes subclavian passage of solution upwards to involve the cervical plexus.

advantages include the fact that a high level of anesthesia may be achieved with a relatively small volume of anesthesia, so if large doses of anesthetic are contraindicated, no supplemental blocks are necessary to limit the volume. In addition, this technique allows the block to be accomplished without moving the painful extremity or shoulder, intravenous injection is most unlikely, and inadvertent subarachnoid or epidural injection is almost impossible.

While it usually can be used in infections of the hand and arm, it probably should not be used in lesions of the neck (or chest) that result in scalene adenopathy. Although pneumothorax, and phrenic and recurrent laryngeal block are not impossible, if the technique is carried out precisely as described, the possibility is extremely remote indeed. Nonetheless, to be perfectly safe, bilateral block should be staggered or accomplished with the axillary technique on one side and subclavian on the other. A minor disadvantage lies in the need to elicit paresthesias with this technique which may be less pleasant for the patient, perhaps, but almost guarantees anesthesia. The subclavian perivascular technique *can* be accomplished without evoking paresthesias, but this requires a great deal of experience and even in our hands results in a 15 per cent decrease in the incidence of success.

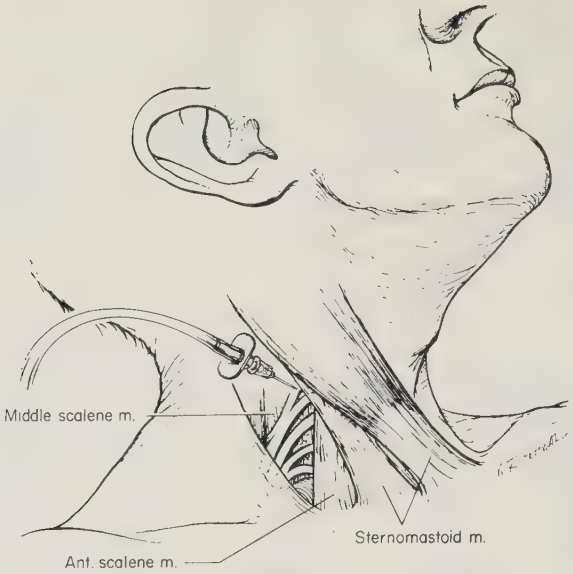


Figure 8. Interscalene technique of brachial plexus block.

Interscalene Technique of Brachial Plexus Block

It was pointed out earlier that as the roots of the brachial and cervical plexuses emerge from their grooved transverse processes, they enter the interscalene space formed by the fascia covering the anterior and middle scalene muscles. Since the majority of this space is above both the subclavian artery and the cupola of the lung, it would seem to be almost an ideal point to perform a brachial block, at least from the point of view of safety.

The technique as we have employed it, is as follows:[17] The patient is in a position similar to that used in the subclavian perivascular technique. The interscalene groove is palpated, and the level of the sixth cervical vertebra is determined by extending a line from the cricoid cartilage laterally to the interscalene groove. At this point, where Chassaignac's tubercle is frequently palpable, a 1½ inch, 22 gauge needle is inserted into the groove perpendicular to the skin in *all* planes (Fig. 8). The direction of injection is thus slightly caudad and dorsad as well as mesiad (Fig. 9). The needle is advanced until a paresthesia is elicited and/or the transverse process is encountered. Once a paresthesia has been evoked the desired volume of anesthetic is injected.

Again the volume-anesthesia relations have been determined by the use of radiopaque dye studies. X-rays taken after 20 ml of dye have been injected into the interscalene space show the dye to be placed slightly higher than the same volume injected into the subclavian perivascular space. Hence, 20 ml of anesthetic injected into the interscalene space results in anesthesia of the lower cervical plexus as well as that of the brachial plexus, but blockade of the ulnar nerve is often delayed and occasionally absent with this volume (Fig. 10*A*).

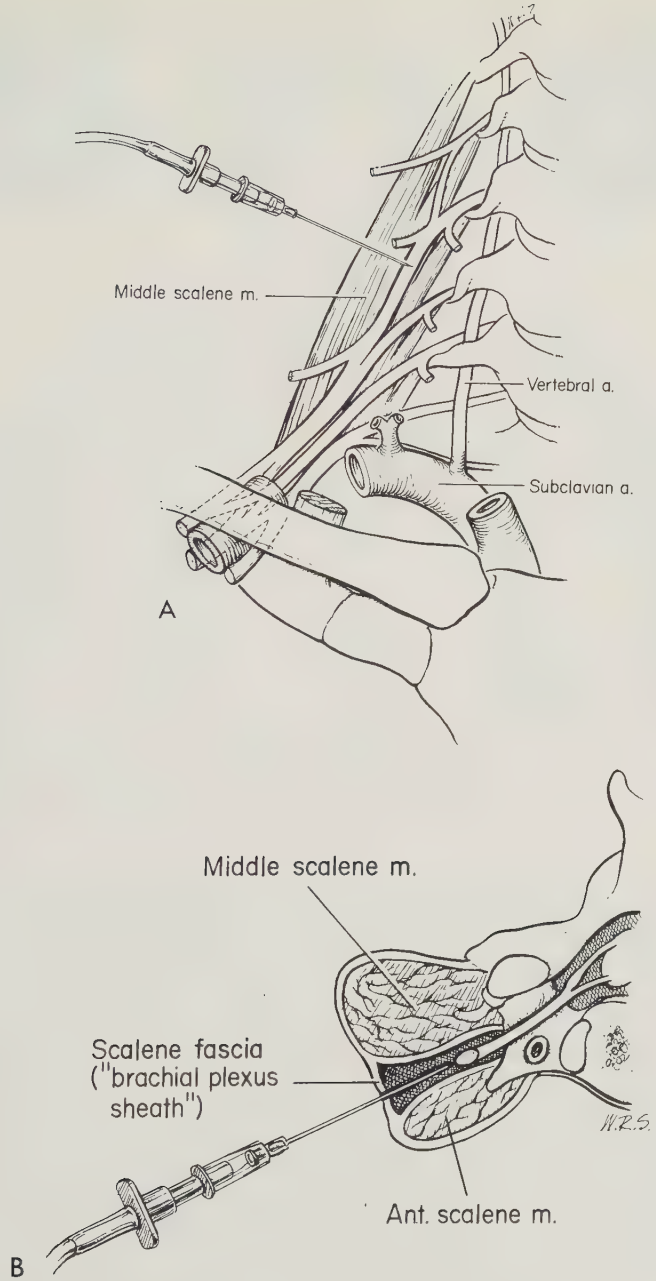


Figure 9. *A*, Frontal view showing needle properly placed for interscalene brachial plexus block. Note importance of slight caudad direction of needle (see text).

B, Cross-section view showing needle properly placed for interscalene brachial plexus block. Note slight dorsad direction of needle.

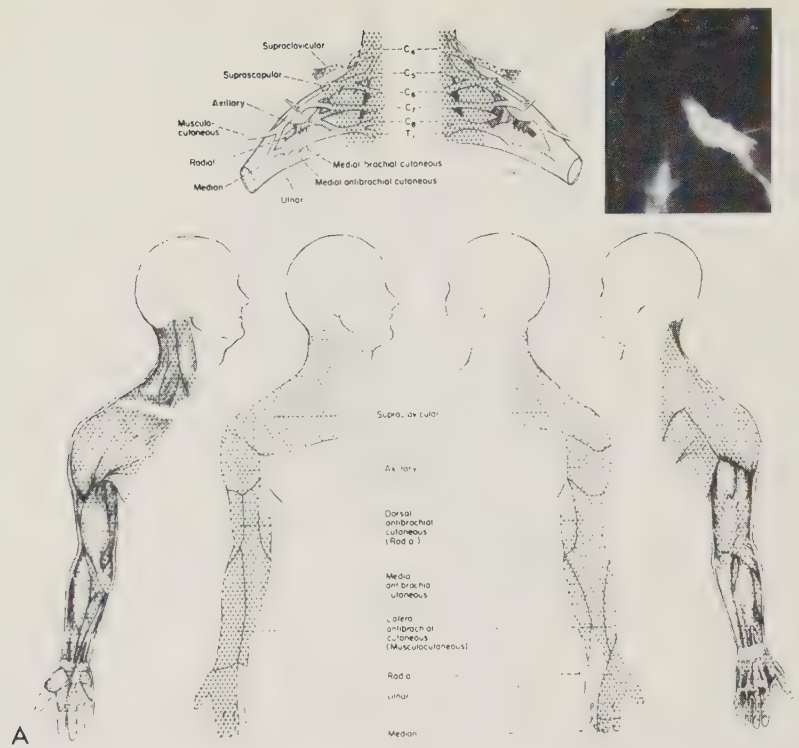


Figure 10. *A*, Volume-anesthesia relationships after injection of 20 ml of solution into the interscalene space. Note absence or delayed onset of anesthesia in distribution of ulnar nerve.

X-rays taken after 40 ml of dye have been injected by this technique show the dye to fill the interscalene space from the transverse processes of the upper cervical vertebrae all the way out to the coracoid process and beyond. Thus this volume of anesthetic injected into the interscalene space will result in anesthesia of both the cervical and brachial plexuses (Fig. 10*B*).

If it is desirable to limit the volume of anesthetic in any particular case, this may be done by blocking the ulnar nerve separately at the elbow. The nerve is palpated midway between the medial epicondyle of the humerus and the olecranon, with the arm flexed. A 25 gauge needle is inserted in the direction of the nerve and when a paresthesia to the little finger is elicited, 5 ml of anesthetic is injected.

If a tourniquet is to be used, the intercostobrachial nerve must be blocked separately as described earlier (see Fig. 4*A*).

The interscalene technique is particularly easy to perform in obese people where the other techniques may be difficult, and is useful in children or intoxicated adults where cooperation is impossible. It is ideal in manipulations and surgery of the upper arm and shoulder where a high level of anesthesia is obtained with a relatively small volume. In addition, pneumothorax is impossible, and this technique can be used in

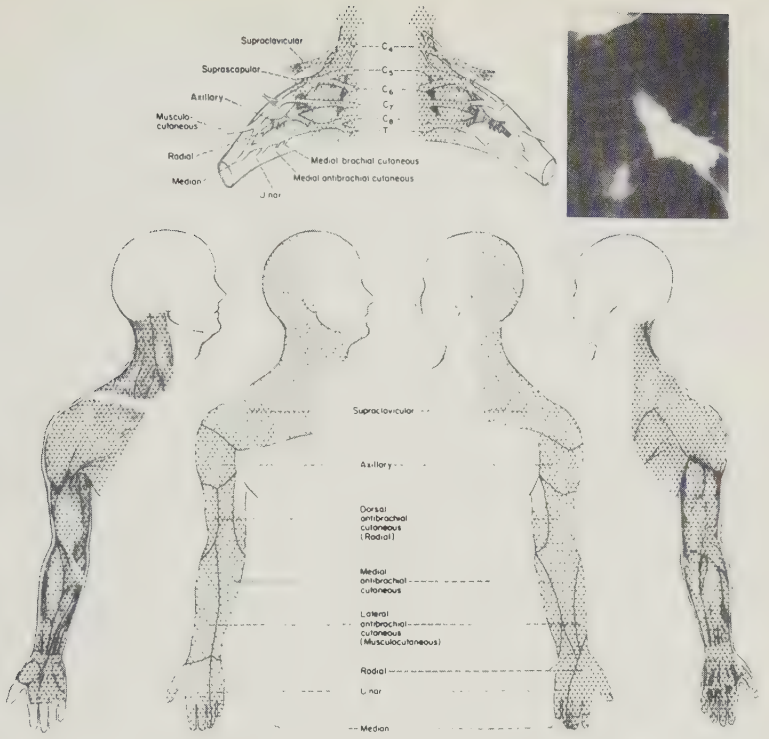


Figure 10 *Continued.* *B,* Volume-anesthesia relationships after injection of 40 ml of solution into the interscalene space. Arrow indicates this volume blocks the cervical as well as the brachial plexus.

infection or malignancy of the arm or chest. The disadvantage of slow onset of ulnar blockade is easy to offset by increasing the volume or blocking that nerve separately. Subarachnoid or epidural injection as well as vertebral artery injection is theoretically possible and several cases have been reported in the literature;[7, 15] but the slight caudad direction of the needle, if carefully observed, should prevent the needle from progressing very far between the transverse processes. Block of the phrenic, vagus, and recurrent laryngeal nerves is not seen if the technique is performed precisely as outlined. Nonetheless, bilateral block should be staggered or combined with axillary block to avoid the slightest possibility of respiratory embarrassment. Naturally, the technique should not be used where there is infection in or trauma to the neck.

Factors Common to All Three Techniques of Brachial Plexus Block

While it is almost axiomatic to say that regional anesthesia is nothing more than applied anatomy, it is equally true that success with regional anesthesia is rendered more certain if one has up his sleeve several of the "tricks of the trade." A few of these "tricks" I feel to be of great enough significance to merit inclusion at this point.

We have emphasized in the preceding paragraphs the importance of the fascia-enclosed space which envelops the various components of the brachial plexus from the cervical transverse processes to the junction of the middle and upper thirds of the upper arm. Thus it has been pointed out that just as with peridural techniques, the extent of anesthesia following a block will depend *primarily* on the *level* at which the anesthetic was injected (the technique which was used) and the *volume* which was injected at that level. However, there are other factors, perhaps less important but nonetheless significant, which can and do influence the volume-anesthesia relationships with two of the three techniques described.

In 1961, when calculating mathematically that 42 ml would be necessary to fill a "cylinder" of the dimensions of the axillary sheath sufficiently to block the musculocutaneous nerve, de Jong *assumed* that the injected anesthetic solution would flow both *up* and *down* the sheath from the point of injection.[3] Obviously, that portion of the agent which flows down the sheath is simply wasted solution, at least in terms of the volume-anesthesia relationships. In an effort to prevent this wasteful retrograde flow, Eriksson placed a tight rubber tourniquet distal to the site of injection just prior to performing the block.[4] To this author such a practice appears both illogical and ineffective. First of all, Eriksson places the tourniquet sufficiently distal to the injection site that, while he may minimize the volume of retrograde flow somewhat, a significant volume of solution is still wasted by flowing from the injection site down to the tourniquet. Secondly, the only reason flow occurs in both directions at all is because the injection is made perpendicular to the long axis of the neurovascular bundle. If the injection is simply made in the direction in which the anesthetist wishes the anesthetic to flow, as in the author's technique, the vast majority of the injected solution will move centrad with very little retrograde flow; and what little solution would flow retrograde when the injection is made centrad can be *completely* blocked by simply applying firm digital pressure immediately behind the needle during the injection. And lastly, the main anatomic obstruction to the central flow of anesthetic solutions injected into the axillary sheath, even with our technique, is provided by the head of the humerus. Dye injections and x-rays have again documented that humeral head obstruction to flow is maximal with the arm abducted to 90 degrees (or more) and decreases until it is nonexistent as the arm is brought down to the side. If one wishes to provide the maximal level possible with any volume, not only should digital pressure be applied immediately distal to the needle *during* the injection, but this pressure should be continued *following* the injection, and after removal of the needle, when the arm should be brought quickly down to the side.

A similar maneuver is useful to minimize the volume necessary in performing an interscalene brachial plexus block. As pointed out earlier, with lower volumes of anesthetic this technique may provide delayed or incomplete anesthesia of the ulnar nerve, while with larger volumes part or all of the cervical plexus will be blocked as well. Thus, if cervical plexus anesthesia is not desirable or necessary for the anticipated procedure, firm digital pressure applied just *above* the needle during the

injection into the interscalene space prevents unnecessary cephalad spread of the anesthetic solution and promotes caudad spread, facilitating blockade of the elusive ulnar nerve fibers in the inferior trunk.

Other factors which quite obviously alter volume-anesthesia relationships are those of height, age, and sex. The basic volume-anesthesia relationships described earlier are the result of studies done on healthy adult males. As with peridural anesthesia, the appropriate volume of anesthetic required to produce a given level of anesthesia will vary with size, and to a lesser extent, with age and sex. Our experience has shown height to be the single most important factor in determining the correct volume for either sex and at any age. This is not surprising, since it is well known that the distance from fingertip to fingertip closely approximates height, so it follows that the height should be related to the length of the "sheath" of the brachial plexus. It turns out that, as a rule of thumb, half the height (in inches) will indicate approximately the proper volume of anesthetic. The calculated volume naturally must be increased or decreased if high or low anesthesia is desired, and the concentration should be decreased somewhat in patients of poor physical status or in infants and children. It is to be understood that this rule of thumb is only a rough guide for the beginner. No rule replaces the clinical judgment obtained through experience, but this one may be useful until such experience has been gained.

In the final analysis, even in the best of hands, success with any nerve block and most certainly with the perivascular technique, depends not only on the precise placement of the needle, but also on stabilization of that needle during the injection of the anesthetic solution. Movement of the needle in attaching and detaching a syringe may dislodge its tip from the desired fascial plane and result in incomplete anesthesia. To overcome this problem we have developed a simple and inexpensive technique which allows complete immobilization of the needle throughout the entire performance of all nerve blocks: A small-bore disposable intravenous extension tubing is interposed between the needle and the syringe containing the anesthetic solution.[16] After the entire sytem has been filled with anesthetic solution, the extension tubing is clamped off and the needle is properly placed for the desired nerve-block procedure. Upon obtaining a paresthesia or after entering the proper fascial plane, the tubing is unclamped and aspiration is accomplished by an assistant (or with the anesthetist's free hand) without movement of the needle, after which the anesthetic is then injected (Fig. 11). If the syringe must be detached, refilled, and reattached, this may be done without moving the needle because of the flexibility of the extension tubing. Worthy of mention is the fact that if care is not taken to fill the extension tubing completely with anesthetic agent, several ml of air may be injected during performance of the block. This is not a serious occurrence, but if the subclavian perivascular or interscalene technique has been used, the presence of this subcutaneous air may lead to the mistaken impression that a pneumothorax has been produced.

This "immobile needle" has been used in hundreds of nerve blocks and has unquestionably enabled us to avoid many failures or partial

Figure 11. The "immobile needle" consists of a piece of flexible plastic tubing inserted between the needle and the syringe so that necessary manipulation of the syringe does not cause movement of the needle.

blocks, particularly in cases where removal of the syringe proves to be mechanically difficult or awkward.

THE INTERSCALENE TECHNIQUE OF CERVICAL PLEXUS BLOCK

Cervical plexus block, even more than brachial plexus block, has continued to be a "cookbook" type of procedure, requiring three to five injections and a large volume of anesthetic solution. Earliest authorities utilized bony landmarks considerably removed from the plexus itself, lines connecting them were drawn, perpendiculars constructed, and needles were inserted at carefully measured distances along these perpendiculars. As is so frequently the case in medicine, once a technique is established, it is handed down verbatim, remaining unchanged for years with the *assumption* that it has a sound and logical basis.

A careful study of the anatomy indicates that (in a manner virtually identical to brachial plexus anesthesia) cervical plexus anesthesia can also be obtained using a *single injection* technique.[22] Since the cervical plexus is invested by the same fascia as that which invests the brachial plexus, cervical plexus anesthesia can also be simply and safely provided by finding the groove between the scalene muscles, and making a *single* injection between these two muscles, but at the levels of C_3 or C_4. X-ray studies taken following the injection of a radiopaque solution at this level have documented the anatomic basis of this technique, which reduces the number of injections, obviates the necessity of blocking both the deep and superficial parts of the plexus, reduces the volume of

anesthetic required, and thus enhances the safety and certainty of the technique. The technique is carried out in an identical manner as was used to perform the interscalene brachial block, except when the interscalene "groove" is located, the palpating fingers move up to the level of C_4, which is determined by dropping a line laterally from the thyroid cartilage (Fig. 12). An injection of 10 to 15 ml of anesthetic made at the point where this line intersects the interscalene groove will provide anesthesia of the entire cervical plexus.

THE INGUINAL PARAVASCULAR TECHNIQUE OF LUMBAR PLEXUS BLOCK

Anatomic Principles

Unlike the brachial plexus, as the nerves derived from the lumbar plexus run into the lower extremity, they lie at a great distance from each other, so much so that in order to produce anesthesia in all of them, multiple separate injections have been necessary to anesthetize each nerve. Furthermore, due to the fact that they are located at a considerable depth, it has been difficult to obtain complete anesthesia, and there has been frequent failure associated with these blocks. Because of the necessity of multiple injections, the difficulty in mastering all three techniques, the prolonged time required to carry out the blocks and produce anesthesia, and the high failure rate, most anesthesiologists prefer the simpler, quicker, and (in most hands) more consistently effective techniques of spinal or peridural anesthesia, if and when

Figure 12. Interscalene cervical plexus block is performed in a manner identical to interscalene brachial plexus block, except that the injection is made at the level of C_4 instead of C_6. (Reproduced from Winnie, A. P., et al.: Cervical plexus block simplified: A single injection technique. Anesth. Analg., 54:370–375, 1975. Used with permission.)

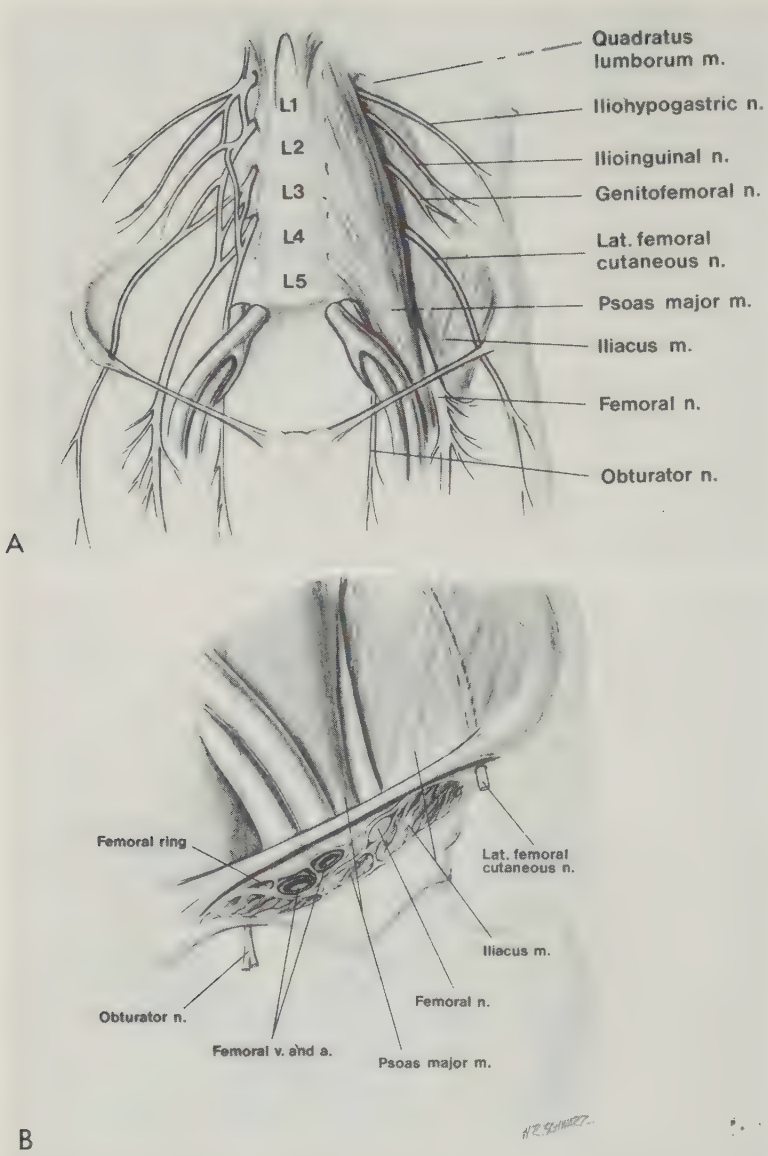


Figure 13. *A*, The lumbar plexus is formed between the quadratus lumborum muscle and the psoas major muscle and hence is enveloped by their fasciae.

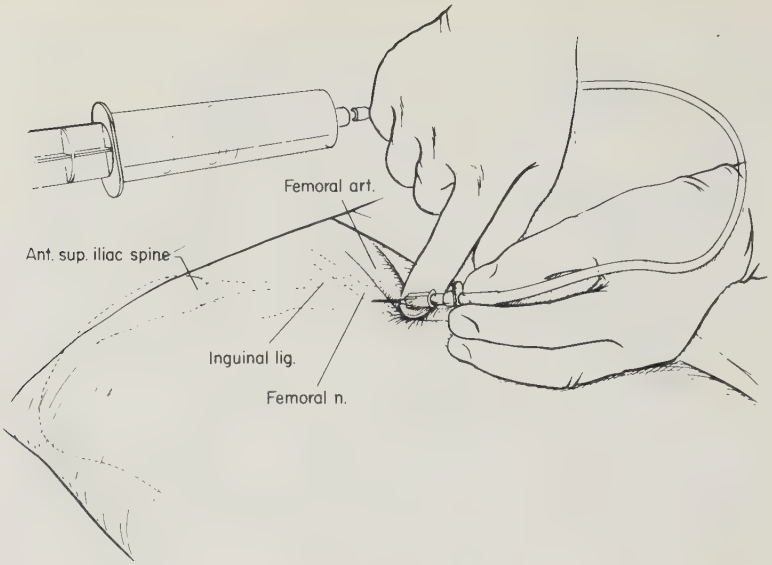
B, A cross-section just below the inguinal ligament to show the fascial compartment surrounding the femoral nerve at this level. Note the thick iliopectineal fascia (unlabeled) which separates the femoral nerve from the femoral vessels. (Figs. 13 and 14 reproduced from Winnie, A. P., et al.: The inguinal paravascular technic of lumbar plexus anesthesia: The "3-in-1 block." Anesth. Analg., 52:989–996, 1973. Used with permission.)

regional anesthesia is indicated for surgery on the upper portion of the lower extremity. However, there are situations in which block anesthesia is the technique of choice. The technique or techniques of blocking the lumbar and/or sacral plexus has been simplified as for the brachial plexus.

The success in developing single injection techniques to produce anesthesia of the brachial and cervical plexuses depended on identification of the fascial plane in which the *formation* of these plexuses took place. While at first glance this would not *seem* possible with the lumbar plexus, a close examination of the anatomy shows that it is. The lumbar plexus is composed predominantly of the first three and the greater part of the fourth lumbar nerves, with an additional contribution being made by the twelfth thoracic nerve. The plexus is formed in front of the quadratus lumborum muscle and behind the psoas major, so as the three major branches begin their descent to the leg, they are sandwiched between these muscles and hence invested by their fasciae (Fig. 13*A*). The femoral nerve, the largest branch to the leg derived from the lumbar plexus, passes down and appears at the lateral margin of the psoas major muscle at approximately the junction of the middle and lower thirds of that muscle. This nerve, unlike the obturator and lateral femoral cutaneous nerves, remains in the groove between the psoas major and iliacus muscles as it continues on its course to the thigh (Fig. 13*B*). Thus, above the inguinal ligament the femoral nerve is bounded laterally by the iliac fascia, medially by the psoas fascia, and anteriorly by the transversalis fascia, so that in its descent towards the thigh the nerve *is* enveloped in a fascial compartment or "sheath." As the nerve passes under the inguinal ligament and into the thigh, the fused iliopsoas fascia continues to provide the posterolateral wall of this "sheath," the inguinal ligament and below it the fascia lata continue to provide the anterior wall, and the thick iliopectineal fascia provides a continuation of the medial wall.

These anatomic considerations would indicate that there *are* certain similarities between the lumbar and brachial plexuses, at least in terms of the way they are formed and their perineural structures: both plexuses are sandwiched between two muscles and hence are enclosed in fascial envelopes as the roots combine to form the respective plexuses. While all three of the nerves from the lumbar plexus remain subfascial as they emerge from the borders of the psoas major muscle, only the femoral nerve carries with it a tubular sheath similar to the axillary perivascular sheath which surrounds the nerves derived from the brachial plexus. However, unlike the close neurovascular relationship in the axilla, where the axillary sheath envelops the whole neurovascular bundle, in the inguinal region the neural and vascular elements are not only spatially separate but their separation is reinforced structurally by the fibrous femoral sheath. This structure ensheathes only the vascular elements and isolates them from the neural and muscular structures below the inguinal ligament.

In view of these anatomic considerations, lumbar plexus anesthesia can also be produced by a single injection, using an anterior, "inguinal *para*vascular approach," in which a needle is inserted into the fascial



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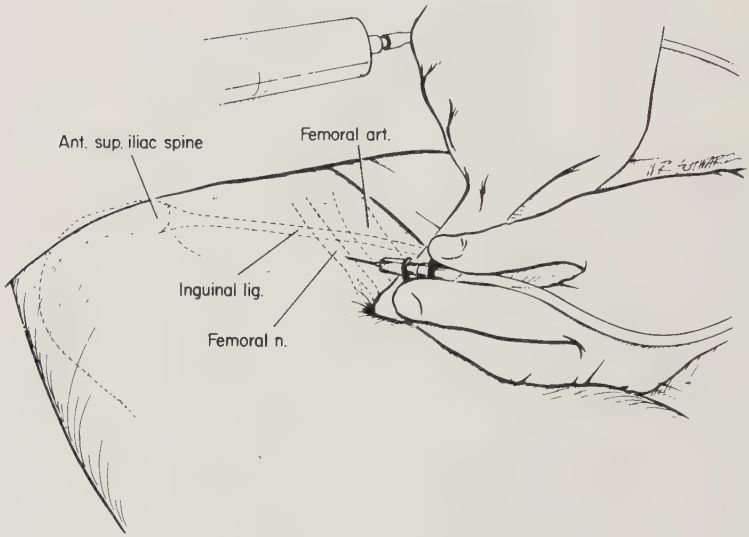

B

Figure 14. *A*, The inguinal paravascular technique of lumbar plexus block is carried out in a manner similar to an axillary perivascular block. The needle is advanced over the finger palpating the femoral arterial pulse until a paresthesia is obtained. (Reproduced with permission of the publisher)

B, When a paresthesia has been obtained the palpating finger is placed behind the needle, where digital pressure is applied during the injection to prevent retrograde flow of the anesthetic. (Reproduced with permission of the publisher)

"sheath" which surrounds the femoral nerve. With this approach the injection is made just below the inguinal ligament and the solution is forced cephalad to block the plexus at the level where the roots lie close together within the same fascial envelope. This technique is carried out in a fashion similar to the axillary perivascular technique of brachial plexus anesthesia: the patient is placed in the supine position, and the anesthetist stands alongside the patient, but on the side opposite the site of the anticipated surgery. After preparation of the skin, with a finger palpating the lateral edge of the femoral arterial pulse, an "immobile needle" is inserted just lateral to the fingertip and is advanced until a paresthesia of the femoral nerve is obtained (Fig. 14*A*). Following the production of a paresthesia, the needle is immobilized while the palpating finger is removed from the femoral artery and placed gently but firmly just distal to the needle (Fig. 14*B*). This is done to prevent retrograde and promote cephalad spread of the local anesthetic as the desired volume is injected. Following the injection the needle is removed but the digital pressure is maintained and cephalad-caudad massage of the area produced. X-ray studies have documented the anatomic basis of the technique, and clinical studies have demonstrated the volume-anesthesia relationships: when volumes of less than 20 ml are injected with the inguinal paravascular technique, the results are unpredictable: to be sure, the femoral nerve will be blocked with this (or a smaller) volume, but the obturator and, even more likely, the lateral femoral cutaneous nerve may be missed. On the other hand, if a volume of 20 ml or more is utilized, anesthesia of all three nerves is virtually assured.

While Bridenbaugh has stated categorically in a recent review of regional anesthesia that "peripheral nerve block is the anesthesia of choice for operations on the *lower* leg and foot,"[2] in the most authoritative text of regional techniques in use today, Moore has emphasized that "open operations on or above the knee cannot be carried out under the combination of sciatic and femoral nerve blocks *unless* the lateral femoral cutaneous and obturator nerves are also blocked." The author goes on to admit that "even in the most experienced hands, blocking of the obturator nerve is often unsatisfactory," and concludes, "therefore, if the patient's physical status dictates that regional analgesia should be employed in these cases, it seems best to resort to a more certain method, e.g., spinal block."[13] Even if block anesthesia is really indicated for surgery on or above the knee, he is saying that the technical difficulty of attempting it and the chances for success are such that it should not even be considered! While it is beyond the scope of this discussion to explore the relative advantages and disadvantages of peripheral blocks, spinal or epidural, or general anesthesia, one would hate to admit that his choice of anesthesia in any case might be affected or altered by technical factors. However, the availability of a simple, safe, single injection technique of lumbar plexus block exists. If an anesthetist is able to provide anesthesia for surgery on the *lower* leg and foot with the combination of a sciatic and femoral block, then he can also produce anesthesia of the *entire* leg by the same combination of blocks, simply by modifying his technique of femoral block (1) by *not* injecting

without paresthesias and (2) by increasing the volume of anesthetic injected.

The use of the inguinal paravascular technique of lumbar plexus block does more than just enhance the simplicity of the anesthesia and increase the extent of anesthesia: it reduces the possibility of adverse side effects; for in attempting to provide block anesthesia of all four nerves using conventional techniques, as many as 10 to 15 insertions of the needle and as much as 65 to 95 ml of local anesthetic may be required. The chance of complications is increased in three ways: first, as with any block technique, the greater the number of needle insertions, the greater the chance of producing neuropathy;[5, 11] it is obvious that the greater the number of injections, the greater the likelihood of intravascular injection; and lastly, the greater the total volume of anesthetic required, the greater is the chance of overdosage and systemic toxicity. By reducing the number of injections required *and* the volume injected, the inguinal paravascular technique virtually abolishes the chances of complications, either neural or systemic.

The inguinal paravascular technique of lumbar plexus block has been shown to be effective in virtually all types of surgery on the lower extremity: combined with sciatic block it is extremely useful in orthopedic and vascular procedures; and used alone, it provides an extensive donor site for skin graft procedures. Since it actually replaces three separate procedures, this technique is easier both to teach and to learn, as is attested to by the fact that the success rate is the same in the hands of either residents or staff.

SACRAL PLEXUS BLOCK

Of all of the nerves derived from the sacral plexus, the sciatic and posterior femoral cutaneous nerves are the most important from the point of view of regional anesthesia, since these two nerves innervate such a large part of the lower extremity. The sacral plexus is formed by the lumbosacral trunk from the fourth and fifth lumbar nerves, and by the first, second, and third sacral nerves. They converge towards the lower part of the greater sciatic foramen, and unite into a large flattened band, most of which is continued into the thigh as the sciatic nerve. The plexus lies against the posterior and lateral wall of the pelvis, between the piriformis muscle and the hypogastric vessels, which are embedded in the pelvic subserous fascia. Since the sciatic nerve is the largest nerve in the body, it certainly should be able to be blocked with a single injection. Because it is usually blocked deep within the gluteal region following "cookbook" types of landmarks, although the injection may be singular, the number of needle sticks required to accurately locate the nerve with the needle is usually multiple. The most commonly employed technique is that described by Labat,[8] which attempts to block the sciatic nerve where it leaves the pelvis through the greater sciatic foramen, i.e., where it lies in the hollow between the greater trochanter of the femur and the ischial tuberosity, sandwiched between the piriformis and superior gemellus muscles. Labat's technique is as follows

(Fig. 15*A*): The patient is in Sim's position, lying on the side opposite the one to be injected. A line is drawn from the superior border of the greater trochanter to the posterior superior iliac spine. This iliotrochanteric line is bisected, and a perpendicular is dropped inferiorly from this line. Up to this point virtually all techniques since Labat's original description are identical; where they differ is with respect to how far down this line the needle is to be inserted in order to obtain paresthesias and make the injection. Some clinicians continue to use Labat's point 3 cm down the perpendicular, some 4,[10] and some as much as 5 cm down this line.[5]

Since the injection is being attempted at a point where the course of the sciatic nerve is still in a somewhat lateral direction (almost parallel to the iliotrochanteric line), then the needle which is inserted too short a distance down Labat's perpendicular will be lateral and superior to the nerve, and the needle which is inserted too far along this line will be medial and inferior to the sciatic nerve. Utilizing Labat's technique (or

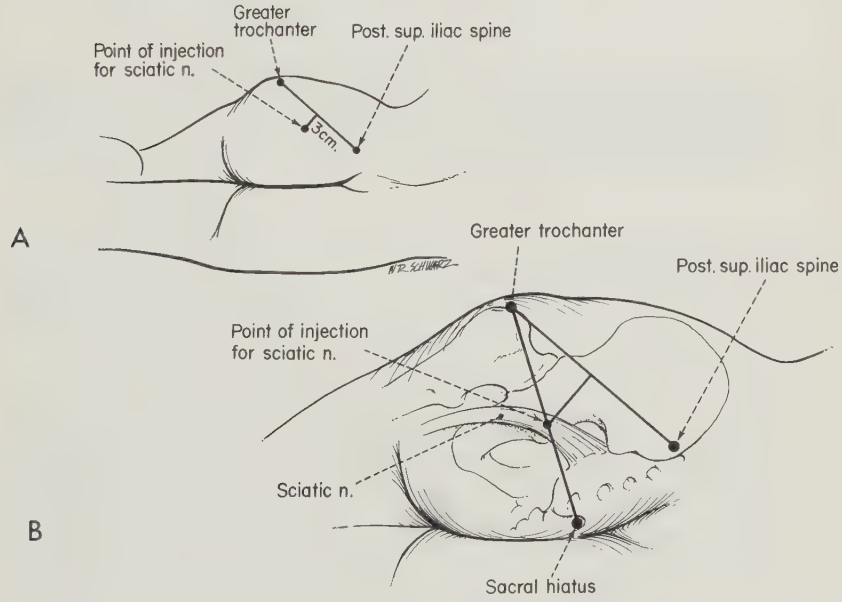

Figure 15. *A*, Labat's technique is the basis of most techniques of sciatic block anesthesia utilized today: a line is drawn connecting the greater trochanter and posterior superior iliac spine, and a perpendicular is dropped from its midpoint. Labat inserted his needle 3 cm down this second line, but disagreement continues as to what is the proper distance along this line (see text).

B, With the author's modification, the distance along Labat's perpendicular at which the needle is inserted will vary with the patient's size. The landmarks are identical to those utilized by Labat except that a second line is drawn from the greater trochanter to the sacral hiatus, and the needle is inserted at the point where this line intersects the perpendicular from the first line. It is obvious that the angle inscribed by the two lines originating at the greater trochanter will vary with the length of the sacrum, which in turn will vary with the height of the patient. (Figs. 15–17 reproduced from Winnie, A. P., et al.: Plexus blocks for lower extremity surgery. Anesthesiol. Rev., *1*:11–16, 1974. Used with permission.)

Figure 16. Supine sciatic block technique. With the patient supine, the hip and knee are flexed by an assistant, who also slightly abducts the hip. A line is drawn connecting the greater trochanter and ischial tuberosity and a 3½ inch spinal needle is inserted parallel to the table in a direction that is perpendicular to the skin in each plane, i.e., mostly cephalad but slightly mesiad. When a paresthesia has been elicited, the anesthetic solution is injected.

any similar technique in which the needle is inserted a *fixed* distance down the perpendicular line), while paresthesias are occasionally obtained after only one or two insertions of the needle at this point, frequently multiple exploratory insertions of the needle are required to locate the nerve and produce a paresthesia. Since the appropriate distance along this perpendicular line varies with the size of the patient, we modified Labat's technique (Fig. 15*B*). After drawing the iliotrochanteric line and constructing the perpendicular from its midpoint, a second line is drawn between the superior border of the greater trochanter and the sacral hiatus; and the needle is simply inserted at the point where this second line crosses the perpendicular. The angle inscribed by the two lines originating at the superior border of the greater trochanter will depend upon the length of the sacrum, and hence upon the height, so with this technique the distance along the perpendicular line will vary with the height of the patient. We have utilized this technique in several hundred sciatic blocks, and have achieved a very high incidence of paresthesias on the first insertion of the needle, with an equally high incidence of success. The reduction in the number of needle insertions has contributed significantly to patient acceptance of this technique, and ultimately should also reduce the incidence of postanesthetic neuropathies. It is interesting to note that the distance along the perpendicular line which results using this technique has varied from 2 to 9 cm, so the importance of a variable site of injection as theorized above would appear to be substantiated. Once the paresthesia has been ob-

tained both the sciatic nerve and the posterior femoral cutaneous nerve, which lie in the same compartment, are bathed with the solution, so anesthesia over the distribution of both nerves results if a sufficient volume of anesthetic solution is used.

While the above modification of the classic sciatic block has enhanced our success rate significantly with this form of anesthesia, like the classic technique, this modification still requires that the patient be turned into the lateral, Sim's position. When it has been impossible to turn the patient to perform a sciatic block, or when such a move would have been extremely uncomfortable for the patient, we have developed a "supine sciatic block,"[21] a technique which may allow block anesthesia to be utilized when it might otherwise be impossible. This technique is carried out as follows: The patient is allowed to remain in the supine position, but the hip and knee are flexed by drawing the heel toward the buttock (Fig. 16). The hip is slightly abducted and flexed to 90 degrees or more, with the knee similarly flexed and supported by an assistant in a position of minimal discomfort to the patient. The ischial tuberosity and greater trochanter of the femur are palpated and a needle is inserted at the midpoint of a line connecting these points. A 3½ inch, 22-gauge needle is inserted parallel to the table (horizontally) in a direction that is mostly cephalad but slightly mesiad as well and is advanced until it encounters the sciatic nerve, which lies at this level in the readily palpable hollow between the greater trochanter and the ischial tuberosity. Following the production of paresthesias along the sciatic distribution, 15 to 20 ml of local anesthetic is injected while firm digital pressure is maintained distal to the injection site.

Other approaches to sciatic nerve block with the patient supine have been described,[1, 6] but we have found both the anterior and lateral approaches to sciatic block to be extremely difficult to accomplish and hence to provide a low incidence of success. The "supine sciatic block" is really a modification of the earliest technique of sciatic block[9] which is simply carried out with the patient in the supine rather than Sim's position. Therefore the level of block is half-way between that at which Labat's approach is carried out in the gluteal region and the level at which the block is carried out in the thigh,[14] but since it uses more easily palpable landmarks and a simpler technique of injection than either of these other techniques and since it does not require that the patient be turned to the lateral position, it may prove to be advantageous in certain cases.

Combined Lumbosacral Plexus Block

If the inguinal paravascular and/or sciatic block techniques are contraindicated (as by infection with inguinal nodes, etc.), if the patient can be turned to the lateral position, and if spinal and/or epidural anesthesia are undesirable or contraindicated, it is possible to block both the lumbar and sacral plexuses by a lumbar paravertebral approach. The technique is carried out in a manner that is almost identical to that which would be used to perform a paravertebral L_4 block, except that following production of a paresthesia, 30 to 40 ml of local anesthetic is injected. Since such an injection is made into the interfascial space between the

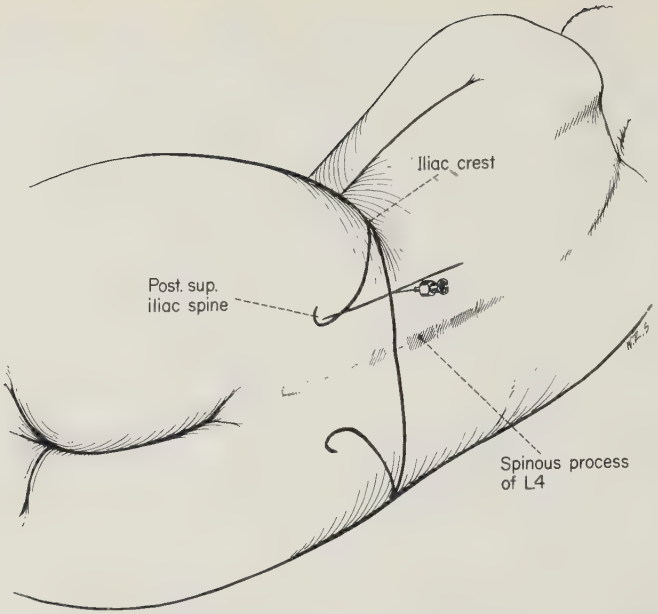

Figure 17. Combined lumbosacral plexus block. With the patient in the spinal position, a line is drawn between the two iliac crests, and a second line is drawn parallel to the spine through the posterior iliac spine. A 3½ inch spinal needle is inserted at the intersection of these two lines perpendicular to the skin, but with a slight mesiad direction. If the transverse process is encountered, the needle is directed slightly more caudad and advanced until a paresthesia is produced, at which point the needle is immobilized and the injection is carried out.

quadratus lumborum and psoas major muscles, the solution dissects caudad and cephalad within this space to produce anesthesia of both the lumbar and sacral plexuses.

The technique is carried out as follows: The patient is placed in the lateral spinal position, lying on the side opposite that to be blocked. A line is drawn connecting the superior borders of both iliac crests, indicating the $L_4 - L_5$ interspace, and a second line is drawn parallel to the spine, but passing through the posterior superior iliac spine (Fig. 17). At the point where the intercristal line crosses the paraspinous line, a 3½ inch, 22-gauge needle is inserted perpendicular to the skin, but with a *slight* mesiad direction. If the transverse process is encountered, the needle is redirected slightly more caudad and advanced until a paresthesia is produced. When a paresthesia has been elicited (about 5 to 6 cm beneath the skin surface) the needle is immobilized, and the injection is carried out. If the transverse process is encountered, the needle is walked off the inferior border of the transverse process until it passes beyond the process and a paresthesia is obtained, at which point the local anesthetic solution is injected. Care must be taken not to direct the needle too mesiad or the needle might enter an intervertebral foramen, resulting in an epidural anesthetic.

EVALUATION

While single injection techniques have overcome the majority of the legitimate objections to regional anesthesia of surgeons, anesthesiologists, and patients, we would be remiss in reviewing these advances if we did not include the tremendous pharmacologic advances which have been made in the area of local anesthetics. With the current availability of local anesthetic agents having a wide spectrum of activity, particularly in terms of duration of action, the usefulness of regional anesthesia has expanded to include areas in which this type of anesthesia was previously unacceptable. Given a group of local anesthetic agents which are capable of providing adequate anesthesia, the limiting factor has frequently been duration of action, at both ends of the spectrum. Today regional anesthetists have available to them anesthetic agents which are capable of providing good surgical anesthesia for a duration of about 20 minutes to about 12 hours, depending on the concentration, addition of vasoconstrictors, and site of injection. Thus, for example, if one wishes to provide anesthesia for a short procedure of 20 minutes duration, the anesthetist may choose chloroprocaine or procaine; for a 1 to 1½ hour procedure, he may choose lidocaine; for procedures which he anticipates may last to 2 to 2½ hours, he may use mepivacaine; for those procedures lasting 4 to 6 hours he may choose to add tetracaine to mepivacaine or lidocaine, with or without epinephrine; and if it is important that the anesthesia and/or analgesia persist from 8 to 12 hours, the anesthetist may choose bupivacaine. The important point to be made is that with such a wide variety of agents available, regional anesthesia is equally appropriate for outpatient surgery, where one wishes the analgesia to be terminated rapidly upon completion of the surgical procedure or in a situation with the hospitalized patient where it is desirable for anesthesia and/or analgesia to persist well into the postoperative period, without the necessity of resorting to continuous techniques or repeated blocks. It is hoped that these newer techniques of regional anesthesia and the availability of these newer agents will allow the anesthetist and surgeon to make available to the patient this very safe form of anesthesia.

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Anesthesia for Cardiac Surgery

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Recent improvements in anesthetic management of patients having cardiac surgery have come about largely because of advances in monitoring and application of pulmonary physiology for respiratory support in the postoperative period. The immediate assessment of changes in the cardiovascular system during induction of anesthesia provides a shorter response time to maintain the stability which is vital in patients with cardiac disease. Continuous monitoring of intra-arterial, central venous, and pulmonary artery occluded pressures is now begun before anesthetic induction. Percutaneous insertion of intra-arterial catheters is a safe and reliable technique for pressure measurement and blood sampling.[5] The radial artery is usually chosen, but other sites such as the femoral or dorsalis pedis may be used.[34] Teflon catheters are preferred because of a lower incidence of thrombosis and catheter over needle design eliminates bleeding from the puncture site.[4] Use of the internal jugular vein for placement of a catheter to monitor central venous pressure offers several advantages.[15] It is a shorter, more direct route than the antecubital approach. It is less likely to produce pneumothorax than the subclavicular route. Inadvertent serious puncture of the carotid artery can be minimized by first using a smaller diameter exploring needle to locate the internal jugular vein. A sterile, dry dressing can be placed over the puncture site which remains out of the surgical field. A cardiac catheter has been designed which can be inserted percutaneously and easily positioned without fluoroscopy.[63] Using this catheter, one can measure the pulmonary artery occluded pressure (pulmonary capillary wedge) which is a reliable indirect assessment of left ventricular filling pressure.[44, 73] This information is highly desirable in patients with cardiac disease because changes in left ventricular performance will often not be reflected early by the central venous pressure and lead to a delay in appropriate therapy.[67] Complications are infrequent and include air emboli, vessel perforation, thrombosis, arrhythmia, and heart block.[20, 39, 76]

More precise control of oxygenation, ventilation, acid-base, and electrolyte status is possible with a clinical laboratory designed specifically for this use in close proximity to the operating room. Arterial Po_2, pH, Pco_2, and serum potassium may change significantly when these patients undergo marked alterations in temperature and circulation. The results must be immediately available to make appropriate corrections.

Preoperative pulmonary function tests and arterial blood gas values are useful in determining ventilatory patterns to be used intraoperatively and as a guide to expected ventilatory function postoperatively. Positive end expiratory pressure (PEEP) may be used intraoperatively to treat pulmonary edema and help maintain patency of small airways.[18]

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PREOPERATIVE EVALUATION

The usual preoperative chart review, history, and physical examination are carried out. In addition, an Allen's test should be performed in both arms to evaluate radial and ulnar flow to determine the best site for radial artery catheterization.[24, 52] A preoperative familiarization with respiratory care procedures by pulmonary physiotherapists and inhalation therapists is extremely useful.

The preoperative orders should be checked for appropriate discontinuation of drugs which may interfere with intraoperative management. They include anticoagulants, digitalis glycosides, and beta-adrenergic antagonists such as propranolol. Digoxin is often discontinued 24 to 48 hours prior to surgery to minimize the possibility of digitalis toxicity due to fluctuations in digitalis and potassium levels seen as a result of cardiopulmonary bypass.[2] Digitalis may need to be administered up to the morning of surgery to control a rapid ventricular response in patients who have atrial fibrillation. Propranolol is usually discontinued 24 hours prior to surgery and some have advocated no administration for 2 weeks prior to surgery.[19] Withdrawal from propranolol may be accompanied by return of angina and result in infarction.[1] If symptoms return after cessation of therapy, propranolol should be given up to the time of anesthesia and surgery. An order is needed for the continuous availability of nitroglycerin during transport to the operating room for patients with a history of angina.

Preoperative sedation may be accomplished with any of a variety of drugs singly or in combination. Barbiturates and narcotics have been classically used and more recently the minor tranquilizers such as diazepam. They are used in reduced dosages in patients with cardiac disease and omitted in those with severe decompensation.

Congenital Heart Disease

The presence of intracardiac shunting of blood affects anesthetic uptake and distribution. An inhalation agent will be taken up from the lungs more slowly in a patient with a right to left intracardiac shunt, thus prolonging the induction phase or requiring higher inspired concentrations.[47] Likewise, removal of this type of agent is delayed, which may create difficulty if an unwanted effect such as hypotension occurs. Intravenous drugs bypass the pulmonary circuit and may facilitate the onset of systemic effects, both desirable and undesirable. Left to right shunting causes a reverse of the above effects on both inhalation and intravenous drugs and is of less concern clinically. Changes in pulmonary artery and systemic arterial resistance may change the degree or direction of shunt.[54] Hypoxia, acidosis, or hypercarbia will increase pulmonary vascular resistance and may even cause the ductus arteriosus to open in the neonate. The percentage of unoxygenated blood in the systemic circuit increases, creating a cycle of additional hypoxia, increasing resistance, and increasing shunt. Likewise, systemic arterial hypotension due to decreased peripheral resistance may favor shunting from right to left, resulting in increased desaturation of systemic arterial blood. The presence of pulmonic stenosis or increased pulmonary vascular resistance as in tetralogy of Fallot will magnify these changes.[54] Many congenital lesions predominantly affect the right heart and pulmonary circulation. This leads to right ventricular hypertrophy, failure, and/or increased pulmonary vascular resistance. During anesthesia changes in cardiac output will be largely due to factors affecting circulating volume, venous return, and pulmonary vascular tone. Fluid administration and positive pressure ventilation must be carefully utilized, and inotropic support given if needed. Acidosis must be corrected promptly.

Aortic Valvular Disease

Management of patients with aortic valve disease centers around changes in systemic arterial pressure. In aortic stenosis relative hypotension may decrease a marginally adequate coronary flow to a hypertrophied left ventricle, leading to myocardial hypoxia, ventricular failure, or arrhythmia which further contributes to hypotension. Tachycardia increases oxygen demand, while decreasing subendocardial supply, resulting in ischemia.[72] Myocardial depression, decreased peripheral vascular resistance, and arrhythmia must be promptly treated as resusci-

tation is very difficult should arrest occur. Patients with this lesion usually tolerate light anesthesia which does not profoundly affect contractility or peripheral resistance. In aortic insufficiency maintenance of adequate systemic diastolic pressure is largely related to heart rate. Bradycardia raises end diastolic pressure and results in pulmonary congestion, as does increasing peripheral vascular resistance.[40] Maintenance or slight increase in heart rate, while decreasing peripheral vascular resistance, should improve cardiac output and decrease the regurgitant fraction.[36]

Mitral Valve Disease

Most patients with mitral valve disease have congestive heart failure which is compensated to varying degrees with a regimen of digitalis and diuretics. Chronic diuretic therapy results in depletion of total body potassium and some degree of relative hypovolemia. Mitral stenosis will result in chronically elevated left atrial pressure, increased pulmonary vascular resistance, and pulmonary artery hypertension. Cardiac output is usually limited by the lesion and is further decreased by tachycardia and hypovolemia. In addition, pulmonary edema may easily occur, resulting in hypoxia. Volume repletion using colloid or blood is often required and high central venous and pulmonary artery occluded pressures may need to be utilized to maintain cardiac output. Mitral regurgitation increases the volume work of both left ventricle and atrium. A decrease in peripheral resistance will promote left ventricular emptying into the systemic circulation and reduce the regurgitant fraction.[22, 25] Inotropic support may also be necessary for the failing ventricle. Atrial fibrillation with an uncontrolled ventricular response is treated with supplemental glycoside. We prefer a drug with rapid onset and short duration, such as ouabain, until the valve replacement is completed and the cardiovascular system is otherwise stable.

Coronary Artery Disease

Most patients in this category have intractable angina with little or no compromise in heart function and undergo aortocoronary saphenous vein bypass grafting.[13] The relationship between myocardial oxygen demand and oxygen delivery is the key issue where oxygen delivery appears to be relatively fixed. Thus the emphasis is placed on decreasing or preventing increases in myocardial oxygen consumption during anesthesia. Tachycardia and hypertension are to be scrupulously avoided as both are significant determinants of myocardial oxygen consumption.[51] These most commonly occur in the anxious patient who is inadequately premedicated and when light anesthesia is in effect at the time of a potent stimulus. Decreasing afterload is beneficial in decreasing cardiac work and oxygen consumption. However, the associated change in diastolic pressure may compromise oxygen delivery and the balance must be carefully maintained. Intraoperative management includes a normal or slightly reduced heart rate, blood pressure near the patient's lowest recorded normal value during hospitalization, and use of anesthetic agents which decrease myocardial oxygen consumption and peripheral vascular resistance.

ANESTHETIC MANAGEMENT

Choice of Technique

Narcotics in large doses are popular as an anesthetic technique for patients having cardiac surgery.[3, 14, 29] Morphine has been most widely used and is basically different from most general anesthetics because it lacks myocardial depressant effects.[70] This property does not necessarily indicate that it is inherently safer than other techniques. Serious hypotension can occur and is due to decreased peripheral resistance and increased vascular capacitance.[30, 48] Intraoperative hypertension can be quite marked and requires additional measures for control.[3] Morphine has been advocated as the anesthetic of choice in severely ill patients who have little myocardial reserve.[75] However, when morphine was compared to halothane in patients having valve surgery without selection for severity

of illness, no difference could be demonstrated in incidence of serious hypotension, mortality, duration of intensive care, or length of hospitalization.[12]

The value of morphine anesthesia in patients with coronary artery disease is questionable. Increases in blood pressure and heart rate are to be avoided. Unstimulated patients with coronary artery disease tolerate morphine very well, but when stimulated by intubation or skin incision, hypertension and an increase in heart rate are seen.[3, 60] Morphine anesthesia is associated with increased catecholamine production which is known to increase myocardial oxygen consumption.[29] Large doses in this group of patients may not produce unconsciousness without supplemental anesthesia.[46]

Morphine anesthesia has been advocated because of the ease of transition to mechanical ventilation postoperatively.[16] This manner of respiratory support has become routine and thus morphine would be advantageous.[45] However, the routine use of postoperative ventilation has been recently challenged, showing that only 10 per cent of patients having valve replacement required ventilatory assistance.[49] Preliminary data from an evaluation of our practice at the Hospital of the University of Pennsylvania support the use of strict criteria in evaluating each patient for the need to support ventilation. The use of large doses of morphine will require respiratory assistance or narcotic reversal because of prolonged central respiratory depression.[35] Thus, morphine anesthesia may not be desirable in patients who might otherwise be allowed to breathe spontaneously soon after the procedure is completed.

Innovar is a combination of droperidol, a butyrophenone tranquilizer, and fentanyl citrate, a synthetic narcotic. Fentanyl has a shorter duration of analgesic effect than morphine and thus requires frequent administration when used as a narcotic anesthetic technique.[61] Changes in the cardiocirculatory system are similar to those observed with morphine or morphine-nitrous oxide. Postoperative respiratory depression may require narcotic reversal or ventilatory support. Narcotic anesthesia has thus gone from wide acceptance to critical appraisal and its place in cardiac surgery is not yet agreed upon by all.

Inhalation anesthesia for cardiac surgery consists mainly of halothane or enflurane in oxygen, with or without nitrous oxide. Explosive agents are limited because of the use of electrocautery and the multitude of electronic devices present in the operating room. Methoxyflurane is seldom used because it is nephrotoxic.

Halothane and the newer halogenated hydrocarbon, enflurane, have similar effects on the cardiovascular system. Both cause myocardial depression which is directly proportional to concentration.[6, 65] Peripheral vascular resistance is not altered or slightly decreased with light anesthetic concentrations. The net effect is a decrease in systemic arterial blood pressure and decreased cardiac output with myocardial depression the predominant cause.[17, 23, 37] Both agents decrease myocardial oxygen consumption.[65, 66]

Potential disadvantages of halothane are association with hepatic necrosis, sensitization of the myocardium to catecholamine-induced arrhythmia, and relative metabolic instability. Ethrane is associated with seizure activity, but at high concentrations and in the presence of hypocarbia. It is relatively stable and less likely to sensitize the myocardium to arrhythmia.[11, 33] Currently there is little to recommend one halogenated agent over another and more information is needed. In general, the resultant myocardial depression and decreased cardiac work may be beneficial, particularly in patients with coronary artery disease. These agents are easily eliminated at the termination of surgery and may find increased utilization if there is no need for prolonged postoperative ventilation in the majority of cardiac surgical patients.

Ketamine is an intravenous dissociative general anesthetic which produces amnesia and unconsciousness with the duration depending on repeated administration. Its cardiovascular effects are mediated by central nervous system stimulation of sympathetic activity which increases plasma catecholamine levels, cardiac output, heart rate, and systemic blood pressure.[32, 56, 64] Its direct effect on the myocardium is depressant.[58] It is associated with vivid dreams and hallucinations which are sometimes terrifying. The incidence is greater in adults than in children and requires a nonstimulating environment in the emergence period

and/or administration of sedatives or tranquilizers.[31, 71] Ketamine anesthesia has been successfully used during cardiac surgery. However, enthusiasm for its use in this field is limited because of the cardiovascular effects intraoperatively and the potential for delirium and hallucination in the immediate postoperative period.

Nitrous oxide is a weak anesthetic in nonhypoxic concentration. It has minimal cardiovascular effects which are direct myocardial depression and increased vascular tone via sympathetic stimulation.[62] Its use in cardiac surgery is to supplement any of the previous major agents.

Neuromuscular blocking drugs are used to facilitate tracheal intubation, prevent movement, and allow controlled ventilation. They are routinely used in anesthesia for cardiac surgery as supplements to any chosen anesthetic agent. Pancuronium is the newest drug of this type. It is a nondepolarizing relaxant approximately five times as potent as curare and more rapid in onset with a slightly longer duration of action. It is easily reversed with cholinesterase inhibitors and its only cardiovascular effect seems to be an occasional sinus tachycardia presumably by a vagolytic mechanism.[57] Pancuronium has largely replaced the use of curare in anesthesia for cardiac surgery because of less significant alterations in the cardiovascular system.

Succinylcholine, a depolarizing drug, is the most rapid in onset and of shortest duration of the muscle relaxants. Its effect can be extended by continuous infusion which is inconvenient in the conduct of cardiac anesthesia. Prolonged infusion also may be associated with uncontrollable duration of block, necessitating prolonged postoperative ventilatory support. Its chief use in cardiac anesthesia is during induction where rapid paralysis is desired and to facilitate tracheal intubation.

There is no technique which is proven clearly superior for clinical management of anesthesia for cardiac surgery. The critical basis for choice remains the skill of the individual anesthesiologist in employing any technique in a given circumstance. Newer agents are being developed and modifications continue to appear in the literature which may lead to an inherently better or safer method.[43, 50, 53]

Induction

A smooth transition to the unconscious state is mandatory in the patient with cardiac disease. Patients with valvular lesions may have a relatively fixed cardiac output. Struggling, coughing, and the resulting Valsalva maneuver may seriously impair venous return and cardiac output. In patients with coronary artery disease, a stormy induction will be associated with hypertension and tachycardia which increase myocardial oxygen consumption. Crying and struggling may affect shunting across a ventricular septal defect and produce marked cyanosis in the pediatric patient. A slow intravenous or inhalation induction is also necessary to avoid sudden changes in heart rate and blood pressure and to allow the anesthesiologist to compensate for the cardiovascular effect of the drugs being administered. Where possible, continuous monitoring of pressures and electrocardiogram will shorten the physician's response time during this critical period. Hypertension and tachycardia can accompany laryngoscopy. Increasing anesthetic concentration and application of topical anesthetic will attenuate this response and lessen similar effects of tracheal intubation.[16]

Maintenance

Anesthesia is maintained as needed with consideration for the marked stimulation of the skin incision and in the case of sternotomy the splitting of the sternum. Administration of volume to compensate for blood loss, vasodilatation, and positive pressure ventilation will be necessary and guided by central venous pressure and pulmonary artery occluded pressures.

Ventricular failure may occur and is evidenced by ventricular dilatation, hypotension, decreased cardiac output, or rising filling pressures in the face of adequate volume status. Therapy is aimed at decreasing cardiac work or increasing contractility. Vasodilators, such as sodium nitroprusside, decrease afterload and promote left ventricular emptying which results in increased cardiac output

and decreased myocardial oxygen consumption.[69] Vasodilatation has been shown useful in congestive failure, mitral insufficiency, and acute ischemia.[22, 26] Increased contractility is accomplished by inotropic drugs which increase cardiac output, decrease heart size, and increase myocardial oxygen consumption. The choice of inotropic drug depends on the effect desired. Currently epinephrine, isoproterenol, and dopamine are used most frequently.[28, 41] All increase contractility but have different secondary effects. Isoproterenol increases rate and decreases peripheral resistance and would be useful where there is an associated bradycardia and systemic blood pressure is not a critical factor. Epinephrine is less likely to increase rate at low doses and causes peripheral constriction as dose increases. It is useful where increased systemic pressure is a desired effect such as ventricular failure in aortic stenosis. Dopamine is the newest inotropic drug which in moderate doses does not affect rate, decreases peripheral resistance and increases renal blood flow.[21] In very high doses it increases rate and constricts the peripheral vessels. Dopamine offers versatility in its effects and may gain popularity as clinical experience increases.

Arrhythmias often occur when the heart is manipulated for placement of perfusion and drainage cannulae. Most will disappear when manipulation is stopped. However, if they persist, pharmacologic therapy or electrical pacing may be instituted. Rapid institution of bypass may also be accomplished instead of the other measures.

Bypass

Anticoagulation is accomplished with heparin prior to bypass. There is no universal protocol for heparin administration or its subsequent reversal with protamine. An analysis of five protocols representative of 30 presently used throughout the country shows failure to anticoagulate safely or neutralize appropriately a significant number of patients.[10] Thus there is a need for individualization of heparin-protamine requirement. The development of a precise rapid determination of heparin effect has provided a means of such individualization and enhanced the accuracy of control of coagulation.[55] This technique has been used sucessfully and most likely will gain wide acceptance as the method of choice in heparin-protamine therapy.[9]

Autologous blood removal and hemodilution are currently used to reduce or eliminate the need for banked homologous blood.[27] Prior to institution of cardiopulmonary bypass, arterial blood is withdrawn from the patient into standard CPD blood bags with simultaneous intravenous replacement with balanced electrolyte solution or colloid (5 per cent albumin or plasma protein fraction). The amount removed is dependent on the calculated hematocrit after institution of bypass using a bloodless prime. In the average adult, 500 to 1200 ml are removed, which results in a prebypass hematocrit of 30 per cent and hematocrit of 20 per cent after mixing with the bypass prime. Decreasing the hematocrit below 20 per cent without increasing pump output will result in inadequate oxygen supply.[38] After bypass is discontinued, the remaining fluid in the reservoir is gradually returned to the patient with simultaneous diuresis causing the hematocrit to rise. Careful potassium replacement during diuresis is essential. After major surgical bleeding is stopped and heparin is neutralized, the autologous blood is infused. This technique is of limited use in patients already anemic preoperatively and in those with poor or no renal function. It has successfully been used to extremes in patients with rare blood types and in those of the Jehovah's Witness faith who refuse any homologous transfusion.

Besides reducing or eliminating the hazards of homologous transfusion, hemodilution offers better flow characteristics, particularly during hypothermia, due to lowered viscosity. A decrease in magnitude of experimental myocardial ischemia has been shown to be associated with hemodilution.[77] The contribution of fresh whole blood to restoration of coagulation factors after cardiopulmonary bypass is another advantage.

Flow rate is maintained at a normal cardiac index while changes in perfusion pressure largely reflect changes in vascular resistance. In normal man cerebral blood flow is directly proportional to mean arterial pressure to 55 torr above which cerebral autoregulation maintains flow constant. Central nervous system

dysfunction has been shown to occur when mean blood pressure is allowed to fall below 55 torr on bypass and is related to the degree and duration of hypotension.[59] Postoperative neurologic deficits have also been related to hypotension during bypass.[68] This lower limit is increased in patients with preoperative hypertension. Upper limits of perfusion pressure are less well defined. However, the patient's calculated mean pressure peroperatively may be used as a guide. Alpha-adrenergic drugs may be used to treat hypotension and chlorpromazine, trimethaphan, or nitroprusside may be used to treat hypertension. Monitoring of mixed venous Po_2 may be utilized as a metabolic index of perfusion. Hypothermia slows metabolic rates and will allow for less perfusion if necessary.

Anesthesia during bypass is maintained by adding volatile agents to the gases flowing through the oxygenator or intravenous drugs to the circulation. Inhalation agents are removed prior to termination of bypass in order to evaluate cardiac function without the effect of depressant agents. If the patient exhibits signs of awareness, additional scopalomine can be given. Once bypass is terminated further anesthetic administration is guided by the same criteria as in the prebypass period.

Immediate Postbypass Period

Preparation for discontinuation of cardiopulmonary bypass includes determination of arterial pH, Po_2, Pco_2, and potassium, return to normothermia, and resumption of mechanical ventilation with 100 per cent oxygen. Adequacy of cardiac function is assessed by observing intra-arterial pressure as a function of gradual increases in central venous pressure, pulmonary artery occluded pressure, or left atrial pressure. If volume is thought to be adequate for ventricular function but arterial pressure inadequate, inotropic support is indicated and a number of agents may be used (see previous discussion of inotropic drugs). The routine use of these drugs prior to observation of spontaneous cardiac action is questionable. The choice before assessment must be arbitrary and no one drug or dose will achieve the optimum effect, and in some cases may be detrimental. All have different effects on rate, rhythm, and peripheral vessels, while increasing contractility and myocardial oxygen consumption as previously mentioned. A reliable rapid method of determining cardiac output would be of value in deciding the need and effect of pharmacologic therapy. Computerized thermodilution cardiac output measurement is a new technique which could be applied.[74] Currently, it is too expensive for routine use and requires a specialized intracardiac catheter.

Intra-aortic balloon counterpulsation offers external support to the left ventricle by increasing aortic pressure during diastole and decreasing afterload.[42] The effect is an increase in coronary perfusion and decrease in cardiac work. It has been used to reverse myocardial ischemia and to increase cardiac output in left ventricular failure. In cardiac surgery its primary role has been in supporting the heart which does not respond to pharmacologic therapy when attempts to withdraw bypass fail.[7, 8]

At the completion of surgery, the patient is transported to the intensive care area with continuous monitoring of arterial pressure and electrocardiogram by portable oscilloscope. Once in the intensive care unit, the need for further mechanical ventilatory assistance can be assessed. This area of care is discussed in further detail by Cullen and Cullen in this symposium.

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Anesthetic Management of Patients with Cardiac Disease

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The perioperative management of patients with severe heart disease has improved markedly in the past decade. Anesthesiologists are now safely anesthetizing patients who, because of severe cardiac disease, would not have been acceptable candidates for surgery 10 years ago. There is every reason to expect this trend to continue. The three most important advances have been made in understanding the cardiovascular effects of anesthetics, perioperative monitoring, and postoperative respiratory care.

What follows is a discussion of the necessary steps in the perioperative assessment and management of the complications of heart disease.

PREOPERATIVE EVALUATION

It is wise to consider the possibility of heart disease in all patients coming to surgery, regardless of age or apparent physical condition. Nevertheless, a high index of suspicion is reserved for groups of patients especially at risk: males, those in middle to old age; cigarette smokers; those with elevated blood pressure, serum cholesterol, and glucose tolerance; those with electrocardiographic changes; and those with a strong family history of heart disease, even when symptoms of heart disease are absent.[31] Therefore, patients in this category must be even more carefully evaluated. A full medical evaluation will usually have preceded the anesthesiologist's preoperative visit. If this has not been done and is not feasible, a cardiac evaluation is performed.

A history of chest pain or shortness of breath on exertion, edema, nocturia, palpitations, syncope, or paroxysmal nocturnal dyspnea are clues to the presence of heart disease. Exercise tolerance, in particular, is an excellent means of classifying severity of impairment. A history of use of digitalis, diuretics, anticoagulants, and antihypertensive agents will often give clues as to the presence of heart disease, and these drugs may profoundly affect the anesthetic course. A history of previous hospitalization and associated disease, such as diabetes, or a family history of cardiac disease are warning flags of possible serious underlying illness.

The physical examination may often provide clues as to the severity of heart disease and complications which one may encounter. Observation of the patient's breathing may warn a careful observer that cardiac illness is present. The blood pressure and pulse are clues in the search for pre-existing hypertensive cardiovascular disease or arrhythmias. Neck vein distention reflects possible elevation of ventricular end-diastolic pressure and suggests congestive heart failure. Auscultation may detect signs of incipient pulmonary edema, with wheezes over

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the anterior upper chest or moist rales at the most dependent portions of the lung. Palpation of the chest for the point of maximal impulse of the heart will reveal enlargement if the impulse is beyond the midclavicular line. Auscultation may detect third or fourth heart sounds or murmurs suggestive of heart disease. The presence of dependent edema is also a sign of congestive heart failure. The chest roentgenogram may show cardiac enlargement or pulmonary edema. Additionally, the electrocardiogram may reveal arrhythmias or evidence of ischemia, pulmonary emboli, or electrolyte imbalance. In patients with congestive heart failure, blood gas determination may reveal unexpected hypoxemia.

When heart disease is suspected, the value of the medical or cardiological consultation cannot be understated. But the cardiologist must understand that the anesthesiologist needs answers to these questions: (1) Is heart disease present? (2) If so, how severe? (3) Is the patient in optimal condition for surgery, and if not, what can be done to improve his condition?

CHOICE OF ANESTHESIA FOR PATIENTS WITH CARDIAC DISEASE

The anesthesiologist strives to maintain the ideal physiologic milieu while rendering the patient insensitive to pain with pharmacologic manipulations. Because all anesthetic agents are toxic, he balances the risk of a particular anesthetic against the need for loss of consciousness and pain relief. The choice of anesthesia for patients with cardiac disease depends upon a number of variables including the familiarity of the anesthesiologist with a given agent and the pharmacologic peculiarities of a specific agent. As a rule, general anesthesia is usually indicated for most cases not involving an area where local anesthesia could be used safely. It has the advantages of quick reversibility and relative ease of blood pressure control, particularly in hypertensive patients. Because the patient is asleep, anxiety with attendant autonomic reflexes is absent.

Conduction anesthesia (either spinal or peridural anesthesia) for cardiac patients has its advocates. However, it lacks the reversibility of general anesthesia. In addition, the agents themselves may, like general anesthetics, cause significant cardiovascular depression.[26] Administration of a conduction anesthetic may result in sudden loss of sympathetic tone in the extremities which may lead to severe, poorly tolerated hypotension. Hence these agents must be used with great caution.

Local anesthesia with specific nerve block may also be used. Their use depends in great part on the expertise of the anesthesiologist and the emotional state of the patient. Again, large amounts of local anesthetic agents can depress cardiac contractility and change intracardiac electrical conduction which may lead to cardiac standstill.

All anesthetic techniques have advantages and disadvantages. All known anesthetics are depressants and no anesthetic is completely safe. In severely ill patients mortality will occur in the best of circumstances. The most important part of anesthetic management of patients with cardiac disease is not the choice of anesthetic agent or technique by itself, it is rather the anticipation of complications and preparation with appropriate monitoring of cardiovascular function. Intensive care facilities may be used routinely for those patients at highest risk in the immediate postoperative period to avoid late and unexpected complications.

INTRAOPERATIVE CARDIAC MONITORING

Patients with arteriosclerotic or hypertensive vascular disease are much less tolerant of even small changes in cardiac output, oxygen carrying capacity, or blood oxygenation than are patients without disease. The basic problem is to permit a heart with compromised function to maintain its own perfusion and that of other organ systems. Monitoring during anesthesia for cardiac patients is, therefore, directed toward the following goals: (1) to follow the effects of anesthetic agents on cardiocirculatory function; (2) to maintain adequate cardiac output and perfusion pressure to avoid damage to organ systems; (3) to maintain adequate

respiration; (4) to maintain a physiologic acid-base and electrolyte milieu. Monitoring systems must allow the anesthesiologist the time to prevent and treat undesirable changes in cardiac output, perfusion pressure, and peripheral resistance before permanent damage occurs.

The severity of cardiac disease, available monitoring equipment, and contemplated surgery dictate the monitoring during the perioperative period. For simple cases, in whom mild disease exists, the routine monitoring equipment may be as simple as a blood pressure cuff, continuous contact with the patient by pulse or stethoscope, and electrocardiographic monitoring. On the other end of the spectrum are those patients with severe cardiac dysfunction in whom beat-to-beat monitoring of left and right sided heart pressures are essential. Left heart activity is commonly clinically assessed by blood pressure measurement with percutaneous placement of an intra-arterial cannula into an accessible artery. We have successfully monitored pressure from such cannulae in the radial, brachial, dorsalis pedis, posterior tibial, and femoral arteries. Minute-to-minute monitoring of blood pressure has been accomplished using Doppler ultrasonic techniques, electronic monitoring of Korotkoff sounds, plethysmography, or oscillotonometry. In our hands, these latter methods have not been as satisfactory as intra-arterial monitoring. Beat-to-beat invasive monitoring of blood pressure should be considered when precise control of blood pressure will be essential, and when dangerous instability of blood pressure is expected.

Starling's law of the heart relates the effect of ventricular presystolic volume on stroke volume.[25] Increasing presystolic volume (which increases ventricular presystolic pressure) increases stroke volume. The opposite also occurs. Left ventricular activity is more important than right in monitoring cardiac output. Hence, it is important to have measurements of left ventricular filling pressures (left ventricular end-diastolic pressure). Because obtaining this directly is impossible in most operating theaters, indirect measurements have been used. Left ventricular filling pressures are reflected by left atrial pressure which in turn is reflected by pulmonary capillary wedge pressure. A catheter placed in a pulmonary capillary wedge position will allow some assessment of left ventricular pressure provided that left atrial pressure is not above 25 torr[29] and that positive end expiratory pressure exceeding the left atrial pressure is not being used. Measurement of central venous pressure by percutaneous placement of a catheter into the central venous system is widely used, easily accomplished,[27] but a less direct reflection of left ventricular end diastolic pressure than Swan-Ganz catheter placement, particularly when left heart failure is acute and when there is no evidence of right heart failure.[28] Volume status is often better ascertained by measuring changes in right-sided pressures after an increment of volume has been given than by using the pressure as an absolute measurement of volume status.

Blood pressure depends directly on the product of cardiac output and peripheral resistance. Though peripheral resistance can be clinically assessed by observing capillary filling of nail beds, etc., it is a technically difficult measurement to make. Yet in some cases it may be of value to know in order to adjust cardiocirculatory therapy. Measurement of cardiac output using dye or thermal dilution techniques allows the calculation of peripheral resistance. Those willing to develop the technical skill necessary to produce dilution curves find it worthwhile. However, it is a skill that atrophies with disuse. The recent introduction of computer derived dilution curves holds promise of facilitating such measurements, once their technical problems can be eliminated and their reliability demonstrated.

Blood gas monitoring during anesthesia has become routine in the anesthetic management of critically ill cardiac patients, particularly to follow oxygenation. The causes of hypoxia during anesthesia have recently been reviewed.[16] For obvious reasons a cardiac patient tolerates hypoxemia poorly. Pulmonary edema occurs more commonly in anesthetized patients with cardiovascular disease, causing hypoxia.[1] When signs of congestive heart failure or arrhythmias develop during anesthesia, blood gas and electrolyte status may be assessed quickly because most clinical laboratories now possess equipment capable of obtaining these values within minutes.

Monitoring of urine output is also of some value in the assessment of circulatory stability. Nearly always, its value depends upon concomitant assessment of other parameters such as blood pressure and venous pressure.

PERIOPERATIVE COMPLICATIONS

It is essential that the anesthesiologist anticipate and prevent the occurrence of the major complications of heart disease. These complications include the following: (1) complications of drug interactions or drug toxicities, (2) arrhythmias, (3) myocardial infarction, (4) hypertension or hypotension, (5) congestive heart failure, (6) pulmonary emboli.

Drug Interactions or Toxicities

Patients with heart disease presenting for surgery often have been treated with antihypertensive drugs, antiarrhythmic drugs, or digitalis preparations. Separately or together, these medications may markedly alter electrolyte balance, autonomic tone, and cardiac performance. In addition, they may interact adversely with many agents commonly used during general anesthesia.

Antihypertensive Medications

During the past decade the debate has continued whether patients should be maintained on antihypertensive medications until the time of surgery. As the pharmacology of antihypertensive agents has become better understood, the consensus has been that the anesthetic course is smoother if antihypertensive medications are maintained prior to surgery (with the exception of the monoamine oxidase inhibitors). It is of value to recognize the effects of each of the commonly used drugs as it relates to anesthesia. Most of the following material is abstracted from a recent, relatively comprehensive review.[8]

THIAZIDE DIURETICS. Thiazide-like diuretics are the most commonly used antihypertensive agents. Because potassium excretion exceeds replacement, a relative hypokalemia, often associated with hypochloremic alkalosis, may occur which may or may not be reflected by low serum potassium concentrations. Severe hypokalemia may lead to muscle weakness, which may potentiate the effects of nondepolarizing muscle relaxants.[21] Hypokalemia affects the electrical activity of the heart so that ventricular rhythm disturbances are more likely to occur, especially in the presence of digitalis. When hypokalemia is a cause of arrhythmias, and renal function is known to be normal, as much as 1 mEq per kg per hr of potassium chloride may be infused under continuous electrocardiographic monitoring, though smaller doses are recommended.[6] Overdosage with potassium may result in cardiac arrest or ventricular fibrillation. Hence, rapid potassium infusion must be maintained only in circumstances permitting close cardiovascular monitoring.

Thiazide diuretics may cause hyperglycemia[22] and uric acid retention which may precipitate gout.[2] As with all diuretics, intravascular volume may become depleted enough to cause hypotension during anesthesia.

NON-THIAZIDE DIURETICS. Included in the non-thiazide diuretic group are triamterene and spironolactone, both of which may be associated with significant hyperkalemia.[8] Acetazolamide, a carbonic anhydrase inhibitor, will lead to electrolyte depletion and metabolic acidosis, but it is seldom presently used.

VASODILATORS. Hydralazine is the only primary vasodilating agent commonly used for chronic management of hypertension in this country today. It is usually used in combination with thiazide diuretics or propranolol. The major danger from this drug is the additive hypotensive effect which may be seen if other depressant agents or anesthetics are used concomitantly. This is usually prevented by reducing dosages of sedatives and anesthetics.

ANTIADRENERGIC DRUGS. Drugs which decrease sympathetic output or responses by a number of mechanisms include Rauwolfia alkaloids, alpha methyl dopa, guanethidine, and beta sympathetic blocking agents. Reserpine, a Rauwolfia alkaloid, acts by depleting norepinephrine stores in the postganglionic sympa-

thetic nerves. Therefore, pressor agents acting indirectly by causing release of norepinephrine, such as ephedrine, metaraminol, and amphetamines, may not be effective when given to patients receiving Rauwolfia alkaloids. Also, anesthetics may potentiate the central sedative effect of reserpine. Hence reduced anesthetic requirements may be anticipated in patients receiving reserpine. With these precautions there is seldom a need for a discontinuance of reserpine preoperatively.[19,20]

Alpha methyl dopa is converted by dopa decarboxylase to alpha methyl norepinephrine which is a false neurotransmitter, resulting in depletion of the normal neurotransmitter, norepinephrine. When a sympathetic nerve ending containing alpha methyl dopa is stimulated, only a weak sympathetic response is elicited. This pharmacologic effect is similar to that of reserpine, but in contrast to reserpine, treatment with alpha methyl dopa increases slightly the effect of both indirect- and direct-acting sympathomimetic drugs.

Twenty per cent of patients receiving alpha methyl dopa develop a positive direct reacting Coombs' test, leading to difficulty in crossmatching blood.

Guanethidine is a potent drug which interferes with the release of norepinephrine from storage sites, causing often profound, orthostatic hypotension. Indirect-acting sympathomimetic drugs may have little effect in patients treated with this medication. There have been no reports of decreased sedative or anesthetic requirements in patients treated with this drug to date. Nevertheless, caution must be exercised whenever depressants are used in conjunction with any antihypertensive drug.

A recent review summarized the available information on the use of beta blocking agents in the perioperative period.[17] Propranolol is presently the only such agent released for use in this country. It acts by interfering with the beta stimulating sympathetic amines. It decreases myocardial contractility. Therefore, when potent anesthetic agents which depress myocardial contractility are used in patients with diminished cardiac reserve receiving propranolol, congestive heart failure may be precipitated. Because it decreases cardiac pacemaker automaticity, it is often combined with other tachycardia-producing antihypertensive agents, such as hydralazine, to maintain a normal heart rate in hypertensive patients. It also interferes with renin release from the renal juxtaglomerular apparatus as part of its antihypertensive activity. In addition, it may precipitate bronchospasm in allergic or asthmatic patients and must be used only with great caution in those patients.

Some controversy has arisen as to whether this drug should be used at all for several days prior to surgery in patients with diminished cardiac reserve because of its depressant effects. The bulk of experience suggests that such patients can be managed safely without discontinuance. The effects of the drugs are normally dissipated within 12 hours after its discontinuance. In the event that beta sympathetic inotropic agents are needed in the course of anesthesia for such patients, increased dosages may be needed.

Monoamine Oxidase Inhibitors. These are seldom used now for control of blood pressure because of the large variety of severe drug interactions which may occur. These interactions include, among others, potentiation of the effects of various anesthetic agents. Severe hypertension or convulsions terminating in death have occurred in patients receiving monoamine oxidase inhibitiors and then given either meperidine or sympathomimetic drugs. These drugs should be discontinued 2 weeks prior to elective sugery[h] and other antihypertensive drugs substituted in the interim.

Digitalis Preparations

These preparations are commonly used to control congestive heart failure, atrial fibrillation, and paroxysmal supraventricular tachycardia. Dosage is sometimes difficult to adjust because of variations in metabolic degradation, bioavailability, and rates of absorption between different brands of the same preparation. Signs of digitalis toxicity may include anorexia, vomiting, visual disturbance, or EKG changes commonly consisting of nodal tachycardia or premature ventricular contractions. However, almost any of the known rhythm disturbances may occur. Overdosage may be first recognized by the occurrence of unstable life-

threatening arrhythmias which may be also associated with hypokalemia. Treatment may include cautious use of intravenous lidocaine, diphenylhydantoin, procainamide, or propranolol, or potassium, depending upon the situation.

Cardiac Arrhythmias

Cardiac arrhythmias are commonly caused by changes in impulse formation or conduction which are exceedingly common during anesthesia, even in the absence of overt cardiac disease.[12] There is at least a 50 per cent incidence during anesthesia in patients with known cardiac disease. Arrhythmias also commonly occur in patients with pre-existing arrhythmias, during intubation, or in patients on digitalis preparations. Most commonly the disturbances are benign, consisting of supraventricular rhythms such as occasional atrial premature contractions or junctional rhythm with atrioventricular dissociation. Though they are benign in most cases, other causes must be excluded when they continue, for their occurrence may be caused by electrolyte imbalance, hypoxia, myocardial ischemia, massive catechol overdosage, and drug toxicity.

Nonaggressive treatment is used when the arrhythmia is not life-threatening (when it is considered relatively stable and is not significantly interfering with either coronary perfusion or cardiac output). In this case, time may be allowed for correction of such underlying causes as hypertension, hypotension, hyperventilation, hypoventilation, or improper depth of anesthesia. More aggressive therapy is indicated during less stable rhythm disturbances such as: (1) ventricular tachycardia;[11] (2) supraventricular tachycardia interfering with cardiac output, causing hypotension; (3) premature ventricular contractions occurring so that the R wave of the premature ventricular contraction falls on the T wave of the preceding beat;[14] (4) multifocal premature ventricular contractions;[14] (5) more than five premature ventricular contractions occurring[14] in a minute; (6) bradycardia causing hypotension or associated with aberrant ventricular arrhythmias.

Nonspecific treatment of arrhythmias must be undertaken only after hypoxia, hypo- or hypertension, or under ventilation have been ruled out as possible causes of the disturbance. Commonly ventricular rhythm disturbances are treated with lidocaine in 50 mg doses with EKG and blood pressure monitoring. Supraventricular tachycardia other than sinus tachycardia is treated with a relatively rapid-acting digitalis preparation or propranolol, depending upon the state of myocardial contractility, electrolyte status, and previous drug therapy.

As with all rules, there are exceptions, e.g., it is well known that runs of ventricular bigeminy or ventricular extrasystoles may occur quite benignly during anesthesia with cyclopropane.[15] Hence, it is always important to consider a cardiac rhythm disturbance in the context in which it occurs and in regard to all events surrounding its occurrence. Treating blindly may precipitate disaster.

Other electrocardiographic disturbances include conduction disturbances such as varying degrees of heart block. High grade heart block occurring during anesthesia may require therapy by decreasing vagal tone with atropine or increasing conduction by beta sympathetic stimulation with isoproterenol. Often pre-existing electrocardiographic evidence of block, such as bifascicular or trifascicular block, will alert the anesthesiologist to prepare atropine and isoproterenol preoperatively or to insert a cardiac pacemaker prophylactically.

Evidence is accumulating that some anesthetic agents depress myocardial conduction and are likely to aggravate mild degrees of heart block.[1, 9, 10, 13] When second or third degree acquired heart block exists, preoperative insertion of a pacemaker should be considered strongly. Although some authorities debate whether such prophylactic insertion of cardiac pacemakers is necessary in asymptomatic patients with acquired bifascicular or trifascicular heart block in whom normal sinus conduction is present,[5] it is our present recommendation that cardiac pacemakers be strongly considered in any patient with trifascicular heart block.

Myocardial Infarction

Development of complications in patients who have sustained a myocardial infarction depends on the number of previous infarctions, the time interval be-

tween the infarctions and surgery, and the functional reserve of the patient. Between 0.2 and 0.4 per cent of all adult surgical patients will develop a postoperative myocardial infarction,[7] the mortality from which ranges between 20 and 80 per cent. If such a patient has previously had an infarct, the mortality is about 50 per cent. A patient who receives anesthesia within 3 months of an infarct is at very high risk of further infarction and death. By 6 months postinfarction, the mortality has decreased to perhaps 5 per cent and remains at 2 to 6 per cent up to 2 years. Unfortunately, the available studies do not describe whether the cause of death in patients who have suffered an infarction is due to arrhythmias, pump failure, or pulmonary emboli, etc. Effective therapy is available if the patient is effectively monitored and treated for the majority of complications occurring after myocardial infarction. These include anticoagulation and antiarrhythmic therapy. The avoidance of unnecessary surgery and close postoperative cardiac monitoring in an intensive care setting will undoubtedly reduce the high risk of coronary occlusion in such patients.

Patients at high risk are those with a long history of exposure to risk factors including previous myocardial infarctions, angina pectoris, diabetes, hypertension, heavy smoking, or electrocardiographic changes suggestive of the presence of coronary artery disease. For patients with unstable angina pectoris no reliable figures of postoperative infarctions are available. In such patients the likelihood of infarction within a 6-month period, even without surgery, may range from 10 to 30 per cent. In summary, a conclusion that can be drawn from the studies of myocardial infarction patients is that proper perioperative preparation and monitoring for patients at high risk from ischemic heart disease should significantly decrease morbidity and mortality. This includes intensive postoperative monitoring for at least 3 days in the case of any patient sustaining an infarction within 6 months prior to surgery.

Hypertension and Hypotension

Many patients with cardiac disease have pre-existing hypertension. Control of preoperative hypertension is necessary if major difficulties are to be avoided.[8, 11, 20] These include the effects of drug interactions between anesthetic agents and the pharmacologic agents used during the anesthesia and instability of blood pressure in the perioperative period. Because of severe vascular disease some hypertensive patients may require much higher than normal blood pressure in order to avoid severe end organ damage such as myocardial infarction, stroke, or renal failure. On the other hand, severe hypertension may lead to intracerebral bleeding, congestive heart failure, myocardial infarction, or severe disturbances of cardiac rhythm due to the inadequacy of coronary perfusion during a time of heavy cardiac work. Uncontrolled hypertension results in a lability of blood pressure during anesthesia which is of major difficulty. If the blood pressure is well controlled preoperatively, the swings in blood pressure during anesthesia are lessened and the problems with severe hypertension postoperatively are reduced as well. Unfortunately, control preoperatively is not always adequate in the presence of pain and fluid shifts postoperatively. Our present approach is to provide adequate analgesia postoperatively when pain occurs, and then treat hypertension not due to pain. Opinion varies as to the best agent to control acute severe hypertension in the operative and postoperative period. Diazoxide, a thiazide antihypertensive agent which acts by causing vasodilatation, has been successfully used for many medical hypertensive emergencies. Side effects may include severe marked hypotension and attendant sequelae, though this is rare.[21] Our preference is for short-acting vasodilating drugs such as steady infusions of nitroprusside or trimethaphan. The onset of action of these agents occurs within seconds and lasts only several minutes after the infusion is discontinued. We prefer these drugs to longer acting preparations both intra- and postoperatively because volume changes, depth of anesthesia or analgesia, and traction reflexes may be rapidly changing.[11] It is often helpful to alter the level of blood pressure control with short-acting agents for events of short duration. Should hypertension continue for a long period, then a longer acting agent can be given when all other possible causes of hypertension have been appropriately treated.

In many instances in the intraoperative period hypertension can be adequately controlled by changing the depth of anesthesia with the aim of maintaining the patient's blood pressure as close as possible to its usual preoperative value.

Patients with cardiac disease have limited cardiac reserve and are often unable to compensate for sudden changes in peripheral resistance or myocardial contractility induced by anesthetic agents or by sudden intravascular volume changes. Perfusion of peripheral organs is normally controlled by a complex biochemical process called autoregulation which somehow decides upon the metabolic needs of a specific organ and then adjusts the blood flow to that organ by altering blood vessel resistance. When blood vessels become arteriosclerotic, the resistance of the vessel is determined by the disease and becomes fixed. The ability to autoregulate is then lost. The perfusion of the area of the organ supplied by that diseased vessel becomes directly dependent on the driving pressure of the blood presented to it. In a normal vessel, when blood pressure falls, autoregulation causes the resistance in that vessel to fall to maintain flow. In a diseased vessel, when blood pressure falls, flow to the area which is directly dependent upon pressure must also fall. This area may then become ischemic. Because of the loss of compensating mechanisms, ischemia is much more likely in the patient with cardiac or vascular disease, and hypotension must be assiduously avoided. This may be accomplished by careful monitoring and use of pressors and volume replacement if quickly needed.

Congestive Heart Failure

Ventricular stroke volume is directly dependent upon ventricular end diastolic volume.[25] A heart which is diseased compensates for falling stroke volume by increasing end diastolic volume which then increases end diastolic pressure. This will be reflected by a rise in the left atrial pressure and pulmonary venous pressure. As pulmonary venous pressure rises, fluid begins to be forced from the pulmonary vascular bed into the pulmonary interstitial space. When the ability of the pulmonary lymphatics to clear this fluid is exceeded, pulmonary alveoli are flooded, resulting in classical pulmonary edema and respiratory failure.

During anesthesia it is not uncommon for congestive heart failure to develop in patients with heart disease for the following reasons.

1. All known general anesthetics suppress cardiac contractility. This may convert a state of marginal cardiac compensation to uncompensated pulmonary edema.[26]

2. Because of surgical manipulations and the type of anesthesia, intravascular capacitance may be changed, resulting in the need for intravascular volume replacement in order to maintain blood pressure and cardiac output. When the anesthesia dissipates, normal vascular reflexes return, leaving the patient with a relative hypervolemia. If the patient is marginally compensated to begin with and cannot excrete the added volume, pulmonary venous pressure may increase to the point of pulmonary edema.

3. The patient may sustain further myocardial ischemia from hypotension or hypertension, leading to a loss of myocardial contractility and resultant congestive heart failure.

Congestive heart failure may be detected by noting wheezes and moist rales on examination of the chest. Other signs will include respiratory difficulty with cyanosis, rising central venous pressure or pulmonary capillary wedge pressure, and hypoxia and hypercapnea as observed with blood gas recordings. Treatment is first directed toward maintaining respiration with supplemental oxygen or mechanical ventilation if necessary. Excess fluid is removed by diuretics, and short- or long-acting cardiac inotropic agents are used, depending upon the cause of the congestive heart failure.

Pulmonary Embolism

The incidence of pulmonary emboli occurring in patients dying of congestive heart failure is as high as 50 per cent.[18] The most likely predisposing cause is stasis due to the decrease in cardiac output, bed rest, and poor perfusion of the

extremities due to peripheral vascular disease. Stasis changes can be diminished by early ambulation, good control of congestive heart failure, and the application of full length stockings to the patient's legs. Anticoagulation is sometimes difficult because of the bleeding from surgical wounds in the perioperative period. Nevertheless, prophylactic anticoagulation in patients at high risk seems reasonable. A number of different techniques for anticoagulation have been recommended depending upon the risk of developing a pulmonary embolus and the surgical procedure.[3, 23, 30]

SUMMARY

The course of anesthesia for patients with cardiac disease includes assessment and management of complications during the entire perioperative period. A thorough understanding of the pharmacology of anesthetic drugs and their interactions with medications taken by patients with heart disease is of utmost importance. The rapid changes in intraoperative circulatory status may often necessitate second-to-second invasive monitoring techniques to maintain stability. Finally, knowledge of complications occurring commonly in such patients allows the anesthesiologist to prepare ahead of time for corrective measures which may be lifesaving.

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Neurosurgical Anesthesia

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A significant number of intracranial operative procedures are performed in patients with an elevated intracranial pressure (ICP) due to tumor, head injury, or hydrocephalus. This article will review our present knowledge of the factors regulating intracranial pressure. The effects of anesthetic drugs and techniques upon these factors will be discussed. An approach is then offered to the specialized problems for patients with intracranial hypertensive or vascular disease, and those requiring surgery in the sitting position, spinal procedures or neurodiagnostic studies.

ICP REGULATION

Lesions are frequently located in the supratentorial compartment or, as in the case of hydrocephalus, exert their effects therein. Therefore, discussion will first center upon supratentorial mass lesions which affect neurosurgical anesthetic considerations. Following this, other neurosurgical problems will be discussed in the context of the principles developed for the supratentorial lesions.

ICP and Intracranial Compliance

The cranium is a semiclosed, nondistensible box. As shown diagrammatically in Figure 1, the contents consist of solid brain matter, cerebrospinal fluid (CSF), and blood. Because these intracranial components are practically incompressible, a volume change in any of these compartments requires that a reciprocal change occur in one or more of the other compartments if the ICP is to remain constant.[25] When a supratentorial mass lesion slowly expands, the CSF usually provides the primary intracranial volume buffer. As the mass enlarges, CSF is transferred from within the skull into the spinal subarachnoid space, dampening the rise in ICP. This CSF translocation requires continued patency of the subarachnoid CSF pathways. Increased CSF absorption may provide further modification of the ICP increase. As the CSF compensatory mechanism is exhausted, moderate reduction in cerebral blood volume (CBV) can provide additional buffering of the potential ICP increase.

These ICP-volume relationships describe a system exhibiting compliance. Compliance may be defined as C = Volume added per pressure change. When a small addition to the intracranial volume incites a large pressure increase the compliance is low and further intracranial volume augmentation will elicit

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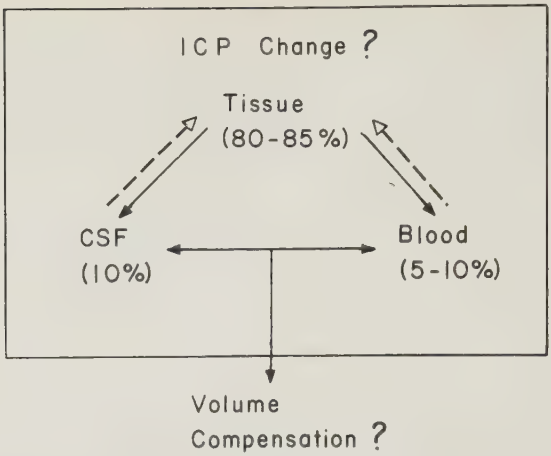

Figure 1. Schematic representation of the major determinants of intracranial volume and intracranial pressure. When any one of the components increases in volume, one or more of the other components must decrease if an ICP increase is to be avoided. Cerebrospinal fluid (CSF) followed by blood volume changes provide the majority of spatial buffering as indicated by the solid lines. If cerebral tissue accommodates an intracranial volume increase (dashed lines) brain herniation or atrophy will follow. The skull is represented by the rectangular box and volume compensation provided by egress of CSF or blood from the cranial cavity. Percentages indicate the relative contribution of each component.

progressively greater ICP increases. These pressure-volume relationships have received much experimental and clinical verification.[38] The clinical utility of ICP measurements can be increased when the state of the intracranial compliance (ICC) is also determined.

Cerebral Blood Volume and ICP

When ICC is reduced, small changes in CBF and CBV can result in clinically significant ICP alterations.[51] CBF and CBV will increase in normally reactive tissue when the P_aCO_2 increases from 20 to 80 torr or the P_aO_2 falls below approximately 50 torr.[5] Between mean arterial pressures of approximately 50 to 140 torr, CBF remains constant (autoregulates) and ICP changes are small.[37] When arterial pressure exceeds the autoregulatory range in either direction, similar directional changes may be expected to occur in the ICP when compliance is reduced. While arterial hypotension can reduce an elevated ICP, it also can cause cerebral ischemia if the lower limit of autoregulation is exceeded. Since the overall cerebral perfusion pressure (CPP = BP - ICP) determines the autoregulatory limits, intracranial hypertension acclerates the potential for cerebral ischemia when the blood pressure also falls.

Intracranial mass or ischemic lesions can alter cerebrovascular reactivity to CO_2 and O_2 as well as adversely affect CBF autoregulation. These lesions incite a buildup in the perivascular hydrogen ion concentration causing a relatively fixed reduction in cerebral vessel tone (vasomotor paralysis).* Consequently CBF, and to a moderate extent ICP, become dependent on the blood pressure. The overall ICP hypotensive effects of hyperventilation (reduced $PaCO_2$) may be reduced as the volume of brain tissue with abnormal reactivity enlarges.

A vicious cycle leading to progressive intracranial hypertension may be established in this situation. A small decline in BP will produce regional or total ischemia whereas an increase in BP can improve CBF transiently. The vasoparalysis permits enhanced transmission of the arterial pressure head into the cere-

*Cerebral arteriole diameter has been shown to be proportional to local hydrogen ion concentration $[H^+]$[65]

bral microcirculation augmenting CBV and ICP. The resulting elevated capillary hydrostatic pressure enhances cerebral edema formation and a further increase in ICP.[26] As the CPP is reduced, CBF falls and eventually cannot be improved by an increase in BP because of the associated rise in ICP. Finally, as the ICP equals the mean BP, CBF ceases.

One often meets a reduced or absent autoregulatory response during trauma from surgery and cerebral compression from tumors, hematoma, and cerebral edema.[4, 44] Control of the BP as well as the P_aCO_2 is thus necessary either to prevent decreases of CBF or ischemic levels, or to abort intracranial hypertension so as to modify swelling of brain tissue into the operative field.

Methods of ICP Control

To provide pharmacologic intracranial decompression prior to surgery, fluid restriction, steroids, osmotic agents and hyperventilation may be required. Although there are few data clearly demonstrating the ICP reduction potential of water restriction alone, it is easily accomplished, relatively harmless, and may potentiate the action of osmotic diuretics.[56] Steroids can be quite effective in reducing ICP over a period of days in patients with primary or secondary cerebral neoplastic diseases.[67] Some patients with brain tumors require very high doses of dexamethasone to sustain consciousness or other neurologic functions. The beneficial actions of steroids in cerebral ischemia or brain trauma remain controversial.

Mannitol infusion and passive hyperventilation may be required to transiently stop or modify acute herniation of the brain.[70] Prior to surgery these modalities are used to gain time to perform needed diagnostic studies. Postoperatively they may be continued along with fluid restriction and steroids. Hypothermia may also be added to the therapeutic regime for its ICP reduction action as well as its ability to offer some degree of protection to ischemic brain.[52]

ANESTHETIC MANAGEMENT OF PATIENTS WITH INCREASED INTRACRANIAL PRESSURE

Preanesthetic Assessment and Medication

The preoperative anesthetic visit prior to supratentorial surgery includes an assessment of the state of intracranial tension, side effects of the intracranial disease and its therapy and the general medical condition of the patient.

Generalized dehydration and attendant intravascular volume depletion frequently accompany aggressive intracranial decompressive therapy, especially if consciousness is already obtunded. Electrolyte abnormalities may coexist. A well documented preoperative body weight is especially helpful during postoperative fluid therapy in patients with reduced consciousness. Patients with decreased levels of consciousness frequently have varying degrees of aspiration pneumonitis and a chest x-ray and blood gases should aid in the clinical assessment of this condition. To guide postoperative therapy, a brief neurologic examination should be done.

At times, pre-existing conditions will require modification of a generally acceptable neuroanesthesia protocol. For instance, an asthmatic patient with an intracranial mass and bronchospasm probably should be given a halothane (ameliorates bronchospasm) anesthetic despite its known intracranial hypertensive action. Immediately prior to administering halothane to this patient, efforts should be directed to reducing ICP and increasing the ICC state.

Intracranial hypertension generally precludes the use of premedicants capable of causing respiratory depression or alterations in the state of consciousness. Atropine may be given to reduce oral secretions. Alert nervous patients with small intracranial mass lesions may be given modest doses of diazepam upon arrival in the operating room to reduce apprehension. Besides providing some amnesia, diazepam has been shown to reduce CBF,[29] to be only a very minor respiratory depressant,[6] and to have anti-seizure activity.[29] Patients not previously on steroids may be given a preanesthetic dose of these drugs since they exhibit their greatest anticerebral effect when given prior to brain trauma.

Anesthetic Drugs and ICP

It was formerly believed that ICP increases associated with neurosurgical anesthetics were caused primarily by poor anesthetic technique leading to hypercarbia, hypoxia, and elevated cerebral venous pressures due to coughing or straining. In 1962 it was clearly shown that halothane could directly elicit an abrupt ICP elevation.[32] Many reports followed, documenting similar actions of other volatile anesthetic agents (trilene,[35] methoxyflurane,[16] and fluroxene[23]). Immediately following these observations, evidence was presented showing that they elevated CBF (and presumably CBV and ICP) in a dose-dependent fashion as effective anesthetic levels were obtained.[37] Experimentally, halothane has been shown to precipitate brain herniation in animals with supratentorial mass lesions.[17] The effects of anesthetic drugs and techniques on ICP, BP, and CPP are indicated in Table 1.

Recently a new volatile inhalational agent, enflurane, was thought to have little effect on CBF after studies in volunteer subjects.[37] However, measurements and observations in some of our patients documented profound reductions in the CPP due to decline in BP, small increases in ICP, or bulging of the brain into the surgical field when under enflurane anesthesia.

Further studies in volunteers and animals have shown that enflurane interferes with autoregulation in much the same way as CO_2 retention.[40] It induces a dose dependent reduction in cerebrovascular resistance. Therefore, the combination of a relatively high dose of volatile anesthetic agent and a sustained or elevated blood pressure can initiate marked elevations in CBF. Presently all currently available volatile anesthetic agents appear to have the potential to elevate ICP when the blood pressure remains at normal or increased levels.

Nitrous oxide can cause ICP elevations in neurosurgical patients, but this effect can be overcome easily by hyperventilation. However, the potency of this action remains unknown since ICC compliance tests were not performed.[21]

Two commonly used intravenous anesthetic agents have clinically significant opposing actions on CBF and ICP. Ketamine elevates ICP[55] and thiopental reduces the ICP increase due to augmented CBV, ketamine and halothane.[54] Hyperventilation also modifies the ICP elevation caused by volatile anesthetics and ketamine.[1, 55] Neuroleptanesthesia provides an alternative to the volatile agents in that small reductions in ICP occur in patients with intracranial lesions with this technique providing the P_aco_2 is not allowed to increase.[15] Nitrous oxide, a short-acting narcotic, and a tranquillizer, coupled with the use of controlled ventilation and muscle relaxants, form the basis of neuroleptanesthesia for neurosurgical patients.

Muscle Relaxants and ICP

When the depolarizing muscle relaxant succinylcholine is given to facilitate endotracheal intubation, muscle fasciculations occurring consequent to its ad-

Table 1. *Clinically Significant Effects of Some Anesthetic Agents on Blood Pressure, Cerebral Blood Flow, Intracranial Pressure, and Cerebral Perfusion Pressure*

	BP	CBF	ICP	CPP
Inhalational Agents				
Volatile Agents	↓	↑	↑	↓
Nitrous Oxide	—*	?—	?↑	?↓
Intravenous Agents				
Ketamine	↑	↑	↑	↓
Thiopental	↓	↓	↓	±↑
Fentanyl-droperidol	↓	↓	↓	—↑

*— means no change.
? means questionable changes.

ministration can cause significant increases in intra-abdominal pressure.[39] Presumably a similar mechanism could increase intrathoracic pressure transiently and thereby elevate ICP. A small dose of a nondepolarizing relaxant preceding succinylcholine can prevent fasciculations.[10]

High doses of d-tubocurarine have been shown to cause intracranial hypertension accompanied by a fall in the BP and CPP.[61] The time course of this reaction incriminates a drug-induced histamine release as the possible cause of this cerebrocardiovascular reaction. A new nondepolarizing muscle relaxant, pancuronium bromide, is less potent in stimulating histamine release and should provide a reasonable alternative to d-tubocurarine in instances of reduced blood volume and/or already increased ICP.

Muscle Relaxants and Acute Hyperkalemia

Succinylcholine administered to patients with peripheral nerve injuries, spinal cord lesions,[60] hemiplegia following stroke,[7] and progressive encephalitis[9] has caused abrupt increases in serum potassium levels. Peaked T waves and ventricular arrhythmias, including asystole, have been observed. Succinylcholine hyperkalemia is most likely to develop within 3 weeks to 3 months following nervous system injury and is believed to be due to an enhanced potassium efflux from denervated muscle with increased motor endplate sensitivity to depolarizing relaxants. To date there are no reports of succinylcholine-linked hyperkalemia in patients with intracranial hypertension. However, the presence of progressive hemiplegia in such patients indicates caution in their use in such instances. A small "defasciculating" dose of a nondepolarizing muscle relaxant probably blunts the subsequent potassium release from denervated muscle but does not make the use of succinylcholine completely safe.[68]

Induction of Anesthesia

Optimal preoperative preparation will bring the patient to surgery with the ICP maximally reduced and the ICC large. Voluntary hyperventilation in cooperative patients just prior to anesthetic induction may aid in obtaining those conditions.

During induction minimal disturbance in intracranial dynamics is desirable. This requires maintenance of a stable hemodynamic state and a clear airway. Since autoregulation may be lost or impaired by the disease process or the anesthetic agent, sudden large changes in blood pressure are to be avoided.

A smooth, rapid, and simple induction is best accomplished by the administration of intravenous barbiturates. Thiopental, slowly administered, produces slight to moderate blood pressure falls. It is a potent cerebral vasoconstrictor, and may reduce ICP by decreasing the CBV.[55] Controlled hyperventilation should immediately follow loss of consciousness.[54]

After a period of controlled hyperventilation, which may be facilitated by long acting nondepolarizing muscle relaxants, a volatile anesthetic agent or drugs such as those used in the neuroleptanesthesia method may be introduced. In many cases hyperventilation improves ICC, and increases cerebrovascular resistance so that the subsequent administration of a volatile agent can be accomplished safely.[54]

Laryngoscopy and intubation can produce a dramatic hypertensive response, especially in patients with pre-existent labile hypertension.[48] Attenuation is achieved by gentleness and total muscular relaxation in a well narcotized subject. Small doses of a ganglionic blocking agent (trimethaphan, 2 to 4 mg intravenously) and/or thiopental immediately preceding intubation will also modify this response. Local anesthesia of the tongue, posterior pharynx, vocal cords, and trachea also reduces the afferent arc of the hypertensive reponse. Relaxation for intubation can be achieved by large doses of a short-acting relaxant, succinylcholine, or with a longer acting drug, such as pancuronium. Figure 2 documents the ICP and BP changes that commonly occur during the induction and stabilization of a neurosurgical anesthetic in a patient with pre-existent intracranial hypertension. Monitoring ICP in such high risk patients can be accomplished by a ventricular catheter[28] or a supracortically positioned subarachnoid bolt.[64] Coupled

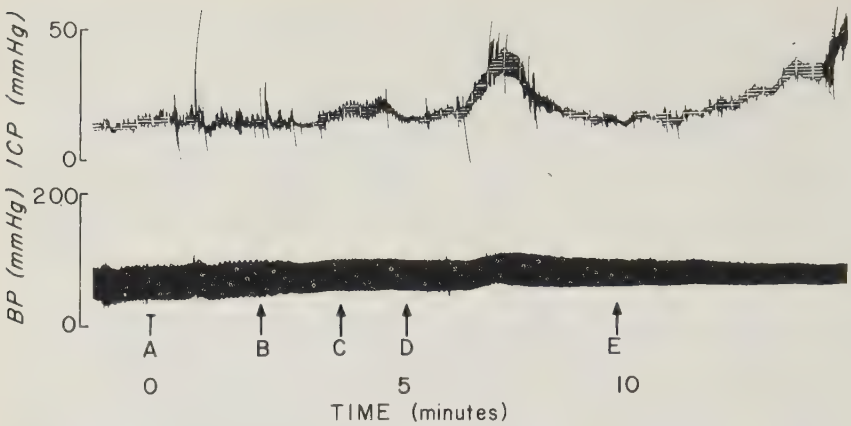

Figure 2. Intracranial pressure (ICP) and systemic arterial pressure (SAP) alterations during the induction and stabilization of anesthesia in a patient with intracranial pathology. Arrow code: *A*, atropine 0.5 mg; *B*, thiopental 250 mg; *C*, thiopental 250 mg; *D*, Succinylcholine 120 mg followed by laryngoscopy and intubation; *E*, begin halothane at 1.5 per cent inspired. Between *B* and *D* there was difficulty in maintaining the airway. The effects on ICP of thiopental, halothane, and airway obstruction are shown.

with continuous measurement of the intra-arterial pressure, moment to moment calculation of the CPP is permitted with appropriate tailoring of the anesthetic technique.

During positioning of the head by the surgeon, care should be taken that no coughing or straining on the endotracheal tube occurs. Adequate muscular relaxation ensures this. Attention is focused on the final position of the neck as excessive flexion or lateral positioning of the head may cause jugular venous compression, increasing the resistance of the cerebral venous outflow and producing venous congestion and an increased ICP. Head movements associated with patient positioning may cause displacement of the endotracheal tube and correct position of the tube should be confirmed.

Maintenance of Anesthesia

An anesthetic technique based upon a volatile anesthetic drug provides potent narcosis, easily controllable anesthetic levels, rapid drug elimination (by ventilation) and the ability to provide the patient with a high percentage of inspired oxygen. Neurolept techniques require nitrous oxide which may effectively limit the inspired oxygen percentage to 30 to 50 per cent. This is considered "light" anesthesia and patients may have recall for intraoperative events. Residual tranquillization, narcosis, and respiratory depression may complicate the postoperative course of a patient given neuroleptanesthesia.

After anesthetic stabilization, mannitol in doses of 1 to 4.5 gm per kg may now be employed to reduce brain swelling and ICP. It is administered intravenously, usually over a 15 to 30 minute period just prior to elevation of the bone flap. This timing avoids the occurrence of any subdural hematomas which may develop as a result of a premature shrinking of the brain resulting in the tearing of the dural sinuses.[31] Mannitol's intracranial hypotensive action begins in 10 to 15 minutes and remains effective for approximately 2 hours. Osmotic agents cause a transient systemic hypervolemia which may precipitate pulmonary edema in patients with cardiac disease.[34] Mannitol dilates resistance vessels and this, together with a concomitant fall in blood viscosity, tends to lower the arterial blood pressure.[66] The fall may be precipitous and severe enough to necessitate slowing the administration rate of mannitol. A Foley catheter should be placed to provide bladder drainage when the use of an osmotic diuretic is anticipated.

POSTERIOR FOSSA LESIONS

Brain Stem Compression and Hydrocephalus

Posterior fossa mass lesions introduce anesthetic management problems directly by compression on the brain stem and indirectly by causing raised ICP due to obstructive hydrocephalus. Medullary compromise, which can be intensified by surgical maneuvers, and its associated cardiovascular instability, is more difficult to detect in the anesthetized-paralyzed patient under controlled ventilation.

Whether or not spontaneous ventilation should be employed during posterior fossa surgery has been strongly debated. Spontaneous ventilation in the anesthetized patient encourages CO_2 retention and vascular congestion, rendering surgery more difficult. It can elicit intracranial hypertension if ventricular CSF drainage has not been provided. Unassisted ventilation performed for prolonged periods in anesthetized patients is associated with progressive atelectasis and hypoxia. In our practice, and in that of several high volume neurosurgical services,[37] controlled ventilation is employed during posterior fossa surgery. Continuous observation of the electrocardiogram, intra-arterial pressure, and end-tidal CO_2 provides information which can be used to monitor surgically induced brainstem dysfunction. Constant communication between surgeon and anesthesiologist is required in this situation.

During anesthetic induction, securing of the airway, and positioning of the patient, care must be taken to prevent extreme movement of the head and neck. With large posterior fossa masses located in a relatively "tight" intratentorial compartment, medullary compression can occur with neck movement.[50] Muscle relaxants and anesthesia increase the possibility of excessive degrees of head movement.

The hydrocephalus secondary to posterior fossa lesions may be associated with high ICP. When ventricular drainage or CSF shunt has been performed several days prior to definitive surgery, this is less of a problem.[34] If the ICP is presumed to be high, the precautions outlined previously should be applied.

The Sitting Position

The sitting position for posterior fossa and cervical spine surgery provides improved surgical exposure, reduced venous oozing, and results in gravity drainage of blood lost in the operative field. However, it introduces the hazards of sudden cardiovascular decompensation and air embolism.

Anesthetics, muscle relaxants causing ganglionic blockade, increased age, intravascular volume depletion, and hypocarbia reduce the ability of the cardiovascular system to compensate when the patient is moved from the supine to the sitting position. In anesthetized patients, small reductions in CBF can occur as the patient is moved to the sitting position even when marked changes in carotid arterial pressure did not occur.[62] When the sitting position is to be employed the anesthetic protocol should be designed to interfere minimally with circulatory reflex adjustments to position changes. The legs and thighs should be wrapped to promote venous return. A light level of anesthesia with a bias toward high sympathetic tone such as a nitrous-oxide-narcotic-relaxant technique and/or low doses of a volatile agent should be provided. Just prior to positioning the intravenous infusion rate may be transiently increased to augment intravascular volume. The actual positioning of the patient should proceed slowly with frequent blood pressure determinations and, if required, judicious use of small doses of cardiovascular stimulants. Ephedrine increases peripheral tone, increases heart rate, and augments cardiac contractility. A dose of 5 to 10 mg is frequently employed for this purpose.

The possibility of venous air embolism is enhanced by the sitting position. Air enters via the exposed cerebral venous system which is at subatmospheric pressure when the head is above heart level.

When air embolism occurs the rate and volume of air entrainment determines the severity of the cardiovascular insult.[58] If nitrous oxide has been employed the volume of intravascular air will be increased as nitrous oxide enters the air bubbles since nitrous oxide is about 30 times more soluble in blood

than nitrogen.[53] Nitrous oxide will be supplied rapidly to the air bubble augmenting its volume. On the other hand, prior denitrogenation by breathing 100 per cent oxygen increases the capacity of the blood to carry the nitrogen component of embolic air in solution. Equal volumes of air administered intravenously at the same rate caused significantly less cardiovascular depression in dogs breathing 100 per cent oxygen, compared to those respired with room air.[58] Furthermore, if nitrous oxide is present when air embolism occurs, not only will it increase the size of the embolic bubbles, but its subsequent elimination by pure oxygen ventilation will be dependent upon the presence of adequate pulmonary circulation. This circulation will be impaired if the air embolism is sudden, of high volume, and causes rapid circulatory decompensation.

As the rate and volume of a continuing or sudden air embolus approaches clinical significance, the amount of air present within the pulmonary circulation exceeds the ability of the lungs to dissipate it. Air embolic blockade of the pulmonary arterial microvasculature then ensues leading to ventilation-perfusion mismatching.[3] Detection of air embolism depends on the magnitude of the process and its effects on cardiovascular function. Continuous monitoring of the end-tidal CO_2 concentration will detect an increase in pulmonary dead space as a decline in end-expired CO_2 levels.[3] When this occurs in the absence of arterial hypotension, it is diagnostic of air embolism. When arterial hypotension accompanies the embolism, the diagnosis of air embolism by end-tidal CO_2 monitoring is rendered more difficult because hypotension also causes ventilation-perfusion abnormalities. The Doppler ultrasound monitor can detect intravascular air when the volume of the embolus is below 1 ml.[30] In practice, although it detects air entrainment that may be clinically insignificant, it serves a vital prophylactic function.

When air embolism becomes clinically significant, cardiovascular dysfunction ranging from moderate hypotension to complete collapse may rapidly ensue. It can be accompanied by the classical clinical sign of a "millwheel" murmur (best detected by an esophageal stethoscope) and/or elevated pulmonary arterial pressure, right axis deviation on the electrocardiogram, and, if the patient is breathing spontaneously, gasping respirations.

Treatment consists of preventing additional air entry at the surgical site by packing the wound and applying bilateral jugular vein compression. Simultaneously, an attempt is made to remove air from the right heart through a previously positioned right atrial catheter; 100 per cent oxygen and vasopressors are administered. Increased airway pressure as a means of elevating cerebral venous pressure is to be eschewed since it also reduces venous return to the heart. Rapid inflation of a "G-suit" may provide transient cardiovascular support during this critical period by increasing venous pressure and return. If cardiovascular performance cannot be restored by these maneuvers, the patient may have to be moved into the left lateral position with the head down to stop air entry, increase venous return to the heart, and alter the position of the "air block" within the pulmonary vasculature.

SUBARACHNOID HEMORRHAGE

When blood extravasates into the subarachnoid space from a ruptured aneurysm, the ICP rises and in effect partially tamponades the bleeding lesion.[41] In some instances the ICP may rise transiently to blood pressure levels and consciousness may be lost due to global cerebral ischemia. Brain death will supervene if this dramatic reduction in the CPP persists for a significant time. As the ICP returns to near normal values after subarachnoid hemorrhage, cerebral ischemia may occur due to vasospasm. Later in the course of the disease, intracranial hypertension may again occur on the basis of a communicating hydrocephalus or rerupture of the aneurysm.

Preoperatively efforts are directed toward preventing rehemorrhage due to hypertension. Sedatives, diuretics, and other antihypertensive drugs are used for this purpose. Intravascular volume depletion and pulmonary complications can occur, especially if the patient is somewhat obtunded.

During induction and maintenance of anesthesia, attention is directed toward maintaining a constant pressure gradient across the aneurysmal sac. This gradient is defined by the CPP. When moderate intracranial hypertension is present due to hydrocephalus the ICP should not be suddenly or drastically reduced as this will reduce its tamponade effect on the aneurysm. Control of the blood pressure by adequate anesthetization and the use of hypotensive agents with transient effects such as trimethaphan or nitroprusside may be required to prevent rerupture during anesthetic induction and stabilization. The BP should be maintained at levels which were recognized preoperatively as safe. ICP measurement during induction of anesthesia aids in determining the CPP and may indicate aneurysmal rerupture.

The agents and techniques employed to obtain arterial hypotension should be easily administered, rapidly effective, transient in action, and should not in themselves cause neurologic side effects. Trimethaphan (Arfonad), a ganglionic blocker, has been very popular for inducing elective hypotension. Tachyphylaxis, occurring especially in young robust patients, frequently accompanies its use. Pupillary dilatation, at times prolonged, may also occur.[20] Sodium nitroprusside, a direct vascular smooth muscle relaxant, has less tachyphylaxis and is a very powerful agent with a transient action time.[63] A number of cautionary reports citing apparent cyanide poisoning (cyanide is produced as an intermediate in the enzymatic degradation process) associated with the administration of very high doses have recently appeared.[36, 63] However, toxicity has not been observed when the hourly dose has been maintained below 200 mg per min.[36] The appearance of apparent tachyphylaxis to nitroprusside accompanied by a systemic acidosis may be a harbinger of impending cyanide toxicity. The employment of other drugs and positioning directed toward potentiating hypotension reduces the requirement for extreme doses of either hypotensive agent. Usually halothane anesthesia and slight head up-tilt achieves this goal.

SPINAL SURGERY

Conditions for which surgery is commonly performed upon the spinal column include degenerative diseases of the disc, intraspinal tumors, infections, and traumatic compression. Degenerative diseases, spondylosis, or cervical spine instability after trauma can complicate anesthetic management by decreasing neck and mandibular mobility rendering oral endotracheal intubation difficult or impossible. The fiberoptic laryngoscope may allow tracheal intubation short of tracheostomy. It serves as a stylet over which the endotracheal tube is threaded after positioning in the trachea.

The positions required for the performance of spinal surgery interact with the anesthesiologist's ability to achieve cardiovascular stability, adequate relaxation, analgesia, provision of a safe airway, and amnesia.

While there is much disagreement as to which position provides the optimal operative exposure for lumbar surgery, the basic tenet of avoiding increased intra-abdominal pressure remains basic to all techniques. Direct abdominal compression must be avoided. The use of muscle relaxants helps this. Faulty positioning invites ocular complications, peripheral nerve and vascular compression, and airway obstruction.

"Awake" oral endotracheal intubation performed under neuroleptanalgesia obtained with fentanyl (short-acting narcotic) and droperidol (major tranquillizer), along with local anesthesia of the pharynx and larynx may come closest to providing the goals set forth above.[18] With this technique the patient remains "conscious" after intubation, turning and positioning himself on the operating table. Leg wraps, employed to promote venous return, and the absence of the cardiovascular depression associated with volatile anesthetic agents promote blood pressure stability. The profound changes in blood pressure so commonly seen when a deeply anesthetized patient is moved are avoided with this technique. The potential hazard of peripheral nerve injury due to avulsive or compressive forces is lessened. After positioning, a sleep dose of thiopental is administered and anesthesia maintained with either a volatile anesthetic or neuroleptanesthesia, and with or without muscle relaxants.

This technique has largely supplanted other induction methods for lumbar surgery in our hospital. Its major drawbacks have been lack of initial patient acceptance (usually overcome by a detailed explanation of the procedures and its goals), the increased time required for anesthetic induction, and occasional unpleasant recall of the induction. If the fentanyl is given too rapidly (more than 0.01 mg per min) chest wall spasm may develop but this is easily relieved by the administration of 20 mg of succinylcholine.

When general anesthesia is induced prior to positioning the patient, low doses of volatile agents, such as halothane, should be employed and frequent checks of the blood pressure made. Intubation of the trachea is required not only to prevent loss of the airway but also to provide adequate ventilation and prevent progressive atelectasis. When the dura is tight due to intraspinal lesions, hyperventilation may provide some decompression, since spinal cord blood flow is sensitive to P_aCO_2 in much the same manner as brain blood flow.[43]

Spinal or epidural regional anesthesia has been successfully employed for lumbar surgery.[33] It provides excellent relaxation and obviates the necessity of an endotracheal tube. Among its disadvantages are poor access to the airway, occasional inadequate analgesia, and lack of acceptance due to the medical-legal implications of performing a block in an area where subsequent neurologic deficit might be due to the primary disease process or surgery.

ANESTHESIA FOR DIAGNOSTIC AND NEURORADIOLOGIC PROCEDURES

General Considerations

Commonly performed procedures include cerebral arteriography, gas contrast studies (ventriculography, pneumoencephalography), brain scans, and myelography. A number of general problems commonly encountered in the neurodiagnostic suite are listed below:[12, 19, 22, 45]

1. The patient may be a poor anesthetic risk. The patient may be comatose, and associated systemic or serious chronic disease states may not be recognized.
2. A dark and unfamiliar environment makes it difficult to observe the patient's color, airway, and the anesthetic flowmeters.
3. There is always the potential threat of an explosion, even though modern x-ray equipment is spark proof. The use of nonexplosive anesthetic agents is mandatory.
4. The hazards of electrocution and radiation threaten both patient and anesthesiologist.
5. The diagnostic procedures are frequently too long and tedious. Fatigue and boredom engender carelessness.
6. Preparation of the patient can be inadequate. Patients are often from wards strange to the usual anesthetic preparation and the patient may arrive unpremedicated and with a full stomach.
7. The radiologic suite provides a working environment which is unfamiliar to the anesthesiologist. Anesthesia requirements often are not considered in the construction of the facilities.
8. Maintenance of a clear airway is difficult when access is poor and numerous postural changes occur. Endotracheal tubes may become kinked.
9. Anesthetic management plans may be falsely based on the premise that the diagnostic procedures cause only a minor physiologic trespass, and there is always the threat of cardiovascular instability due to the sudden positional changes.
10. Often the patient is transported to the x-ray department unattended by any medical personnel and left.
11. X-ray rooms are usually poorly ventilated and anesthetic gases may accumulate, reaching unsafe concentrations.
12. Radiologic technicians in their efforts to speedily accomplish a study may not recognize the need to communicate their plans to the anesthesiologist.

Local Anesthesia and Sedation

Neurodiagnostic procedures may either be performed under local anesthesia

with or without sedation, or under general anesthesia. Controversy still exists as to which method best fulfills anesthetic and radiologic requirements.

Local anesthesia is a safe technique and combined with appropriate sedation provides a calm, awake, and cooperative patient. Verbal contact with the patient is maintained and changes in levels of consciousness and physiologic responses to the examination can easily be observed and evaluated. Sedation may be achieved with the following drugs used singly or in combinations: narcotics, butyrophenone derivatives (droperidol), phenothiazines, and benzodiazepines (diazepam). The narcotics are associated with vomiting, cardiovascular instability, and respiratory depression; the phenothiazines with hypotension; the butyrophenones with dysphoria and extrapyramidal effects. Neuroleptanalgesia (droperidol and fentanyl) carefully administered avoids most of the above and is widely and safely used. Droperidol has an antiemetic action which may be useful during encephalography. Diazepam is a potent and short-acting tranquillizer with the properties of minimal cardiovascular, respiratory depression, and a good amnesic action.[13] Local anesthesia with sedation, however, is not the method of choice with young children, mentally deranged or uncooperative adults, and the comatose restless patient.

General Anesthesia

General anesthesia meets many of the requirements needed for the success of the radiologic examination. It provides an immobile patient facilitating the production of clear x-ray films, blunts reflex movements of the patient during injection of the contrast media, and spares the patient the emotional stress encountered during prolonged, sometimes painful investigations. The radiologist can proceed with leisure and safety without patient cooperation. The disadvantages are the same as those discussed previously. Endotracheal intubation performed in children always carries a risk of inducing laryngeal edema and croup. Ketamine, an intravenous anesthetic agent, produces a state of "dissociative anesthesia-analgesia," and provides certain advantages over inhalationally administered general anesthesia. The induction is rapid and smooth, and the airway is usually maintained during postural changes. There is apparent cardiovascular support due to catecholamine release, and respiratory depression is rare and transient. When first introduced, it seemed to offer a promising alternative to endotracheal intubation in children[8] but despite usual maintenance of the airway during ketamine anesthesia, protection against aspiration cannot be assured.[46]

The use of ketamine has a number of implications for the neurologic patient. It greatly increases ICP in patients with mass lesions or hydrocephalus and probably should not be employed when intracranial hypertension is suspected unless ventricular drainage is established.[55] Ketamine also augments brain electrical activity to the point of inducing seizure discharges in experimental animals. It has been suggested that it could complicate the management of patients with a convulsive diathesis.[69]

Cerebral Angiography

Cerebral angiography can be performed by the direct percutaneous puncture of the extracranial cerebral vasculature or via retrograde catheterization of the carotid, subclavian, brachial, or femoral artery. Each method has its own advantages and disadvantages. Local complications relating to the puncture site commonly occur, including hematomas and peripheral neuropathies.

The incidence of cerebral complications caused directly by angiography include dislodging of a plaque or thrombus, air emboli, and subintimal injections leading to compression of branching vessels.[14]

Meglumine iothalamate (Conray) is now the most commonly used contrast medium. As with previously used iodine-containing contrast media, adverse reactions, local and general, may occur. They are usually mild and transient. These include psychosomatic reactions (nausea, vomiting, headaches), arterial spasm, an intense burning sensation during injection, anaphylaxis (rare), and cardiovascular reactions involving mainly minor disturbances (thrombophlebitis, flushing). However, serious neurologic (convulsions, syncope, hemiparesis, asphasia, blindness) and hemodynamic (hypotension, bradycardia, and cardiac dysrhythmias) complications can occur.

There is an increasing tendency to use the N_2O-O_2 relaxant technique for cerebral arteriography in all cases (whether ICP is raised or not) in preference to spontaneous ventilation with a volatile agent. Recovery from nitrous oxide anesthesia is rapid, permitting early re-evaluation of neurologic states. It is claimed that mild hypocarbia (35 to 25 torr) improves the quality of the angiographic films as well as producing a greater delineation of the nonautoregulatory tumor blood vessels.[11] The effect of anesthetic agents and P_aCO_2 levels is shown in Figure 3. However, overzealous hyperventilation could diffusely narrow cerebral vessels reducing cerebral circulation time and give the false impression of diffuse vasospasm. Halothane anesthesia reduces the blood pressure making percutaneous vascular catheterizations more difficult.[27]

No matter what technique is employed, constant monitoring of the BP, pulse, and respiration is mandatory during and after injections of the contrast media until one is satisfied that all systems are stable. Hypotension occurs, perhaps due to baroreceptor discharge, and it is usually mild and transient. However, profound falls in blood pressure can occur particularly in patients with cerebrovascular disease and subarachnoid hemorrhage.[19] Commonly observed cardiac dysrhythmias include bradycardia, ventricular extrasystoles, nodal rhythms, and transient asystole in association with injection of the contrast media.

Contrast Encephalography

These diagnostic studies are accomplished by injecting a contrast agent into the subarachnoid space and maneuvering its distribution in order to obtain an outline of the cerebrospinal fluid cavities. Most commonly, air or oxygen is employed as the contrast agent, although iodinated compounds are also used. The major anesthetic problems are associated with the contrast injection and subsequent positioning and include alterations in CSF pressure dynamics, ventricular size, and cardiovascular status.[12] Even when the study is performed under local anesthesia, resuscitative facilities should be immediately available as the studies in themselves can provoke a broad spectrum of physiologic responses.

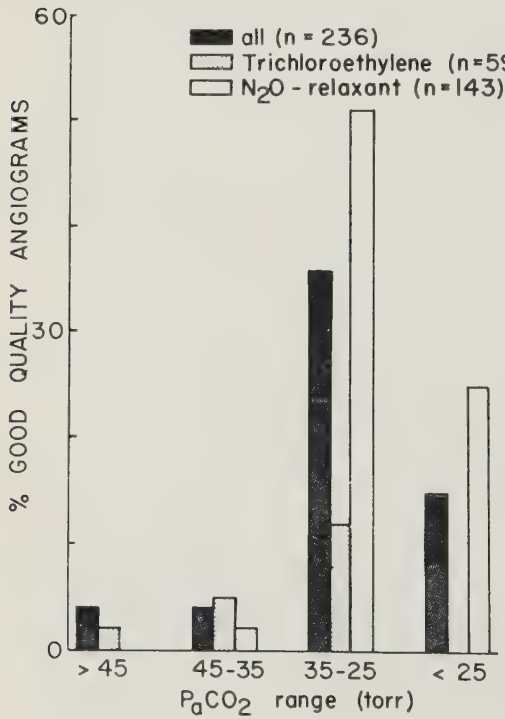

Figure 3. Effect of P_aCO_2 and anesthetic agents on the quality of cerebral angiograms. Constructed from data published by Dallas in reference 11. Optimum P_aCO_2 improves the quality of angiograms, while the volatile anesthetic modifies the effect of hyperventilation by causing vasodilatation.

Pneumoencephalography

This is performed by the slow, incremental injections of air or oxygen into the lumbar subarachnoid space with the patient in the sitting position. It is usually carried out in the absence of raised ICP and the conditions for which it is undertaken include epilepsy, senile dementia, hydrocephalus, and tumors (gliomas of the brainstem, corpus callosum, etc.).

Ventriculography is usually performed on patients with obstructive hydrocephalus and those with raised ICP in which lumbar encephalography is considered too dangerous. When Conray is employed for ventriculography, it introduces a possible side effect of seizures.[17] The intraventricular injection of this agent bypasses the blood brain barrier. There is consequently a 400- to 1000-fold reduction in the seizure threshold compared with intraarterial injections of this agent.[24]

Frequently gas encephalographic studies are accomplished under local anesthesia and mild sedation. The sedation should not be so deep as to cause respiratory depression or dull circulatory reflexes.

However, if the patient is too young or ill to cooperate or if the procedure is expected to be overly distressing and prolonged, general anesthesia may be indicated. A number of specialized problems are now encountered.

Due to the high solubility of nitrous oxide in blood it will rapidly equilibrate into an air-filled ventricle, thereby adding to the intracranial volume on a relatively uncontrolled basis. Since air embolism can also occur as air is injected into the lumbar theca for pneumoencephalography, a number of investigators feel that nitrous oxide should not be used during air encephalography. When nitrous oxide replaces air as the contrast agent there is no contraindication to using nitrous oxide as an anesthetic gas. The relatively rapid removal of nitrous oxide from the ventricular cavity limits the time of the study to about 1 hour. Since air, if it is used, remains in the ventricles headache and nausea are likely to persist.

Generally, anesthesia for encephalographic procedures should be managed as for the anesthetized sitting patient. Despite the potential cardiovascular depression associated with halothane anesthesia, it has been successfully employed during encephalography in a large number of clinics. In one series of patients undergoing air contrast studies, blood pressure decreases of up to 25 per cent were noted with 2 per cent halothane in oxygen. This was accompanied by increases in cardiac output of 25 to 50 per cent with the assumption of head-up positions. Because halothane anesthesia requires endotracheal intubation for safety in these circumstances and is associated with a slow recovery time, a number of alternative techniques have been suggested. Ketamine rapidly induces general anesthesia, characterized by maintenance of the airway and circulatory stability. Probably its use should be restricted to infants with open fontanelles in whom the risk of endotracheal intubation complications is high, or in patients with ventriculostomies providing a means of CSF drainage for ICP control. The dysphoria associated with its use in adults limits its usefulness among adults. Another means of avoiding halothane and nitrous oxide is to use a combination of intravenously administered thiopental and lidocaine to achieve anesthesia. After topically anesthetizing the trachea, intubation is performed, and ventilation with 100 per cent oxygen remains spontaneous.[19] Thiopental reduces ICP and provides amnesia, while lidocaine depresses the cough reflex, produces analgesia, slight sedation, and in low doses cardiovascular-respiratory stimulation. The airway and spontaneous ventilation are maintained as evidence of neurologic function. Provided the dose of thiopental is carefully controlled and the study is not excessively long, a return to consciousness will occur within 1 to 2 hours after the study.

Brain Scans

These studies are noninvasive and require only that the patient remain still during the scanning process. Patients with movement disorders and uncooperative patients will require anesthesia. The recently introduced computerized axial tomographic scan, popularly called the EMI scan, carries with it the additional need to position the patient's head within a metallic cylinder that subsequently encloses the skull within a tightly opposed water-filled bag.[2] Some patients become claustrophobic when this is done and may require sedation and assur-

ance. When anesthesia is required for these procedures we employ a thiopental nitrous-oxide relaxant technique with oral endotracheal intubation. The chief anesthetic hazard with the EMI scan is the possibility of the endotracheal tube kinking against the metallic ring of the head holder or within the pharynx as the patient is moved.

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Problems in Geriatric Anesthesia

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Until comparatively recently the aged were so few that little thought was given to them as a group. They were just old people—wise or childish, feeble or well preserved. By the unescapable statistics of census takers, we are forced now to study the process of aging as well as the economic and social problems of the aged. Surgery has much to offer the aged and the few facts presented... suggest that this offer can be made with considerable confidence.[44]

This statement is even more true today than when it was made in 1948. The magnitude of growth in the geriatric population is clearly outlined in Figure 1.

There are no problems that are unique to the geriatric patient. Rather, the same problems which must be considered in the anesthetic management of any patient, must be considered in the geriatric patient. The differences are quantitative rather than qualitative, for "no disease results from the passage of time and from time only."[8]

One problem which must be considered initially is the definition of the geriatric patient. While a diplomatic definition of geriatrics might include those "older than the patient to whom you are speaking," this definition leaves much to be desired. In fact, there are series of cases reported in which the cutoff age for "elderly" has varied from 45 to 90![11, 46] However, with the advent of Medicare, 65 years has been rather arbitrarily defined as the onset of the geriatric age and the term "senior citizen" has been introduced to denote such a person.[8]

The main reason for variability in criteria is that the aging process is not strictly a function of chronologic age. The young octogenarian who stands straight and walks quickly may be in much better physical shape than the old sexagenarian. Osler long ago emphasized that physiologic age correlates better with the degree of vascular disease than the chronologic age.[38] However, there is no known absolute method to distinguish chronologic and physiologic age at this time and each patient must be considered as an individual.

In an excellent review of aging and pharmacodynamic principles, Bender points out that aging reduces and delays gastrointestinal absorption, impairs and delays renal excretion, and reduces enzyme induction

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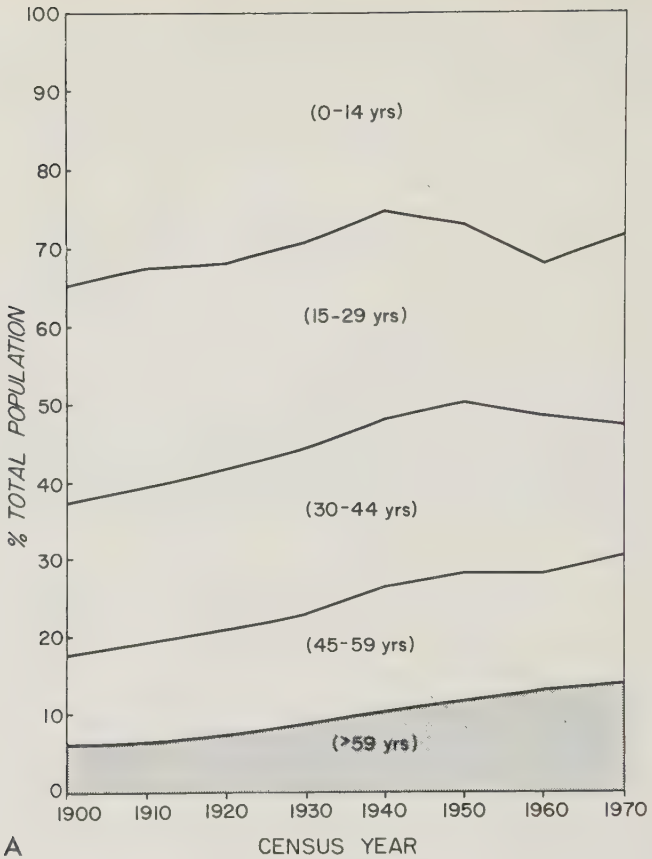

Figure 1. *A*, Per cent distribution of population by age from 1900 to 1970.

rate. In addition, an altered number of receptor sites and a decline in homeostatic capability combine to make drug responses in older persons comparable to those noted in the very young. For example, serum antibiotic levels are elevated after intramuscular administration in the young because of undeveloped renal function and in the aged because of declining renal function.[2] This concept of increased sensitivity to various agents argues strongly for minimizing the number of pharmacologic agents employed and using reduced amounts.

Growth of the Geriatric Population

Figure 1 illustrates the increasing magnitude of the geriatric population. From Figure 1*A*, we see that the per cent of the population over age 59 has risen steadily from 6.5 in 1900 to 13.2 in 1970. This steadily increasing percentage is superimposed on the absolute increase of the population of the United States over the past 70 years (Fig. 1*B*). The combined effect has increased the population over 65 years of age from 2.8 million in 1900 to 20 million in 1970.

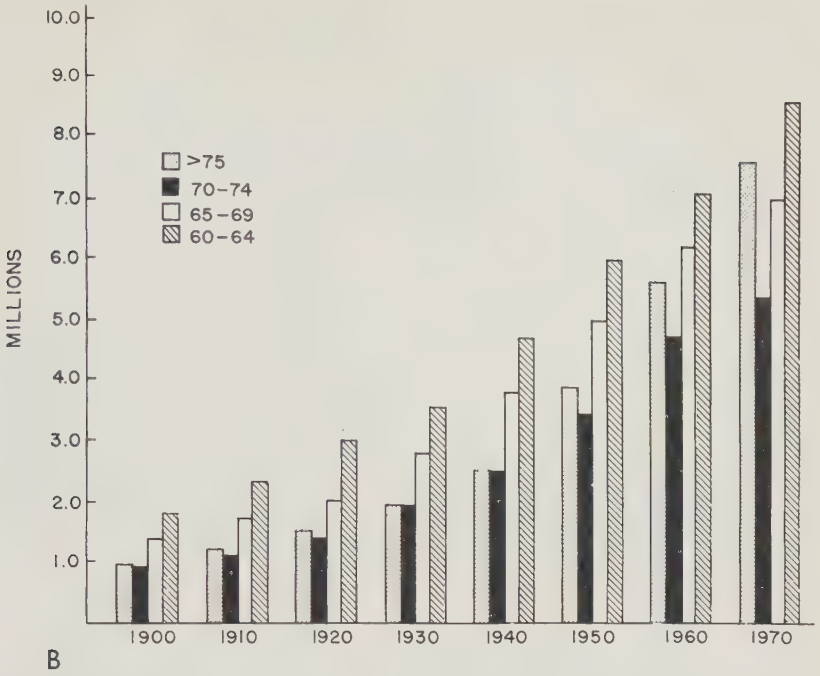

Figure 1 *Continued.* *B*, Absolute population by age group vs. decade from 1900 to 1970. (Data in Fig. 1 from: United States Bureau of the Census Statistical Abstract of the United States: 1971, 92nd ed. Washington, D.C., U.S. Government Printing Office, 1972. Table 53.)

The number of geriatric patients appearing on operating room lists increased sharply with the advent of Medicare, with as many as 33 per cent of such beneficiaries undergoing surgical procedures annually. The five most common procedures in this patient population are (1) cataract extraction, (2) transurethral resection of the prostate, (3) herniorraphy, (4) cholecystectomy, and (5) reduction of fractured hip.[31]

A further reason for the increase in geriatric surgery is the improved results attainable with modern surgical and anesthetic techniques. Clearly, advanced age is no longer an absolute contraindication to surgery. Until recently, operations which were strongly indicated before age 65 were considered contraindicated after that age. This most certainly is not the case today.[21]

In the face of the steady increase in the number of older patients in the past 70 years, we might ask ourselves what factors will ultimately limit this trend. Figure 2 shows the remaining life expectancy at different ages for the past five decades. It can be seen that for the newborn, from 1920 to 1967, there is an increase in life expectancy of 16 years. However, in the 65-year-old group during the same period, the increase was only 3.5 years. Burch states that the cure of cardiovascular and renal disease would add only 7.5 years to the life expectancy and the cure of cancer would add only 1.5 years. Furthermore, the real problem limiting man's longevity is the aging process itself. It is this fundamen-

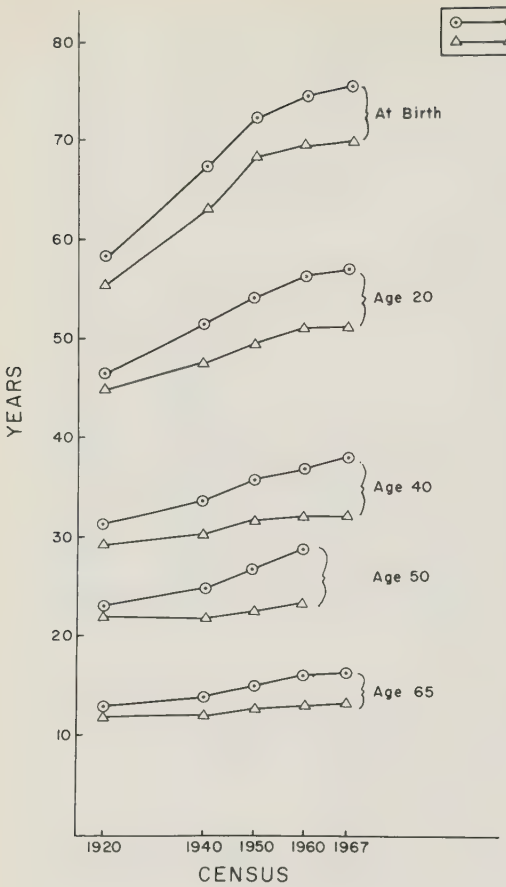

Figure 2. Life expectancy of white females and males by decade from 1920 to 1967. (Data from: United States Bureau of the Census Statistical Abstract of the United States: 1971, 92nd ed. Washington, D.C., U.S. Government Printing Office, 1972. Table 70. Data not available for age 50 in 1967.)

tal process which must be attacked if man is to prolong life further and improve the quality of health.[4]

In a study of aging vs. epidural dose requirements, Bromage demonstrated that dose requirements decrease in a linear manner after the age of 18.5 years and theoretically would reach 0 at age 137 years.[3] These decreased requirements may be related to a diminished complement of neurons and this perhaps implies that by 137 years of age (on the average) the neuronal population within the central nervous system would be so depleted as to cut off communication with the external environment. Obviously, any scheme for prolonging life would be pointless unless there was some way to halt the decline and fall of the central nervous system.

A NARROW MARGIN OF RESERVE (OR "THE ELDERLY NORMAL")

The human body is capable of maintaining homeostasis by varying cardiac, pulmonary, or renal function. For example, cardiac output or

minute ventilation may be increased as much as fivefold in a healthy young male. Similarly, in a dehydrated patient, urine output may fall to less than 10 ml per kg per 24 hours, while a patient who has been volume overloaded may have an output more than five times that much. Unfortunately, this capacity to adapt by extremes of function is progressively impaired with aging. This decline in function has been attributed to a decrease in the number of functioning parenchymal cells, particularly in tissues with poor capacity for division and replacement, such as nervous system or kidney.[42]

In fact, old age has been described as "a continuation of life with decreasing capacities for adaptation."[28] The reduced function in the aged of various organs usually can be demonstrated only by stress testing. Thus, cardiac output which is sufficient for the octogenarian while leading a sedentary life, will not suffice for the same individual during the postoperative period should he become febrile or anemic. An equally important consideration is the fact that all organs do not regress to the same degree. Examples of this are the vigorous man with advanced organic brain syndrome and the arthritic cripple who remains mentally alert. As the adaptability to stress becomes ever smaller with increasing age, both surgeon and anesthetist must strive to avoid wide deviations in vital function.[27]

With respect to pulmonary function, Comroe et al. have defined the "elderly normal" as the man or woman over the age of 50 or 60 years with normal lungs upon physical and x-ray examination and without symptoms of cardiopulmonary disease.[7] However, pulmonary function testing of these patients would reveal the pattern outlined in Table 1. Whether this pattern is the result of physiologic aging of the lung or a succession of unrecognized minor pulmonary infarctions and/or injuries incurred in the preceding four or five decades is not known. Regardless of the cause, the end result is a somewhat enlarged lung at rest, with decreased elasticity, and with reduced maximal movement.[39] The adverse effect of age on pulmonary function is demonstrated by the following equations:

Vital capacity (males) in ml $= 27.63 - (0.112 \times \text{age}) \times$ height in cm

MBC (males) in l per min $= 86.5 - (0.522 \times \text{age}) \times$ BSA in sq meter

Table 1. *Pulmonary Function Patterns in the "Elderly Normal"**

Lung volume:	decreased vital capacity, increased residual volume and functional residual capacity, and increased residual volume to total lung capacity ratio (RV/TLC) from a normal of 20 per cent to 35 to 40 per cent.
Ventilation:	slight decrease in frequency, tidal volume, and minute volume; increase in anatomic dead space; decrease in oxygen consumption and CO_2 production; normal response to inhaled carbon dioxide and 100 per cent oxygen.
Distribution of inspired gas and blood:	more uneven with increased alveolar dead space.
Pulmonary circulation:	essentially normal.
Diffusion:	decreased maximal diffusion capacity for oxygen.
Arterial blood:	oxygen saturation, pH, and CO_2 are usually normal.

*Adapted from Comroe, J. H., Forster, R. E., DuBois, A. B., et al.: The Lung, Clinical Physiology and Pulmonary Function Tests, 2nd ed. Chicago, Year Book Medical Publishers, Inc., 1962, pp. 212-213.

These patients need not have symptoms in spite of marked change in pulmonary functions. Nevertheless, the changes produced by relatively mild pulmonary disease superimposed upon the pre-existing changes associated with aging may well result in severe symptomatology because of the narrow margin of reserve.

The volume of the lung at which small airways begin to close has been defined as the "closing volume" (CV). At volumes below CV, gas will be trapped in the alveoli served by these closed airways, resulting in arterial desaturation. Among the factors which determine CV, e.g., body habitus and position, increased age has been shown to correlate well with increased closing volumes.[13]

Cardiac output is closely related to total body oxygen consumption at rest and during exercise. Progressive decrease in resting cardiac index with increasing age may well indicate limited cardiac reserve, another example of the narrowed margin of reserve in the geriatric patient.[37]

Prolongation of circulation time with advancing age has been demonstrated. This has practical implications for the anesthetist inasmuch as slower circulation time may lead to overdose of an intravenous induction agent unless rate of injection is reduced. Similarly, the onset of paralysis following injection of a muscle relaxant may be delayed.[18]

Preoperative prophylactic digitalization has been advocated for elderly patients based on the assumption that, though they may endure the strain of sedentary day-to-day activities, their compromised cardiac performance ("presbycardia"), may fail with the added strain of surgery.[13] This remains a most controversial area. Indeed, several studies have indicated that many institutionalized patients on long term digitalis therapy demonstrated no deterioration of cardiac function when digitalis was discontinued.[19]

Progressive decline in renal blood flow and renal function has been demonstrated as manifested by decreased glomerular filtration rate and concentrating ability.[42] Such a reduction in renal function ordinarily necessitates a larger urine volume with comparable nitrogen load than in the younger individual in order to prevent nitrogen retention. Furthermore, the combination of decreased renal and cardiac function makes the more careful titration of volume and fluid replacement in the geriatric patient mandatory.

Renal excretion of drugs such as induction agents, relaxants, and digitalis may also be impaired.[2]

PRE-EXISTING DISEASE

Figure 3*A* plots the average number of physician visits per year versus age for male and female. With the exceptions of the first year of life and of females during the child-bearing age, there is a steady rise in the frequency with which patients seek medical attention as they age. Incidence of disease may reasonably be expected to parallel the number of physician visits per year. Thus, aging patients undergoing surgery

can be presumed to be more likely to have pre-existing systemic disease than their younger counterparts.

The contribution of pre-existing diseases to surgical mortality has been documented in numerous studies. Cogbill found a fourfold rise in mortality in aged patients with pre-existing disease (2.6 vs 10.8 per cent) and a twentyfold increase if the pre-existing disease process was acute (44.1 per cent).[5] Indeed, the related disease may actually affect the prognosis of life even more unfavorably than the contemplated surgical procedure.[47] While this is undoubtedly true, the opposite viewpoint has been taken by some: namely, very old patients simply by their longevity have demonstrated a strong constitution, and hence the nonagenarian may be a better risk in some ways than the septagenarian.[34] Figure 3*B* illustrates the prevalence of four common diseases as a function of age. Each of these diseases may present problems for the anesthesiologist as well as the surgeon. Hypertensive patients may be taking various medications, diabetics may be taking insulin, and patients with rheumatoid arthritis may be taking steroids or other potent medication. Clearly, pre-existing diseases and current medication must be considered in planning the anesthetic management.

Another potential hazard possibly due to related disease is that of misdiagnosis. Howie, in pointing out that the diagnosis of appendicitis is more difficult in the elderly, argues for greater willingness on the part of the surgeon to operate when the diagnosis is in doubt since the death rate in unnecessary appendectomy is less than in perforated appendix.[24] Attributing symptoms of appendicitis to other disease processes such as peptic ulcer or gastritis seems more likely in the elderly.

HAZARDS OF THE EMERGENCY PROCEDURE

The mortality rate in emergency surgery may be as great as five times that for elective procedures.[26] Two main factors contribute to this increased mortality rate: (1) the patient's tardiness in seeking medical attention results in a more advanced disease process than would be the case had elective repair been performed, and (2) the lack of time permitted to control pre-existing disease may result in the patient being brought to the operating room in less than optimal condition.

Furthermore, elderly patients have an especially poor tolerance for complications that are more likely to occur during emergency procedures. It is imperative even in emergencies that ample time be taken, although with a sense of urgency, to study and prepare these patients adequately. Examples of this would include the preoperative digitalization of patients in congestive failure or the correction of electrolyte imbalance as well as crossmatching and administering blood to correct significant anemia. Lorhan found that in 60 patients with fractured hips operated upon within 12 hours of the fracture, the mortality rate was 42 per cent; 491 patients operated upon more than 12 hours after the fracture had a 25 per cent mortality rate. Intraoperative circulatory instability was reported in most of the patients in the under 12-hour group. Cor-

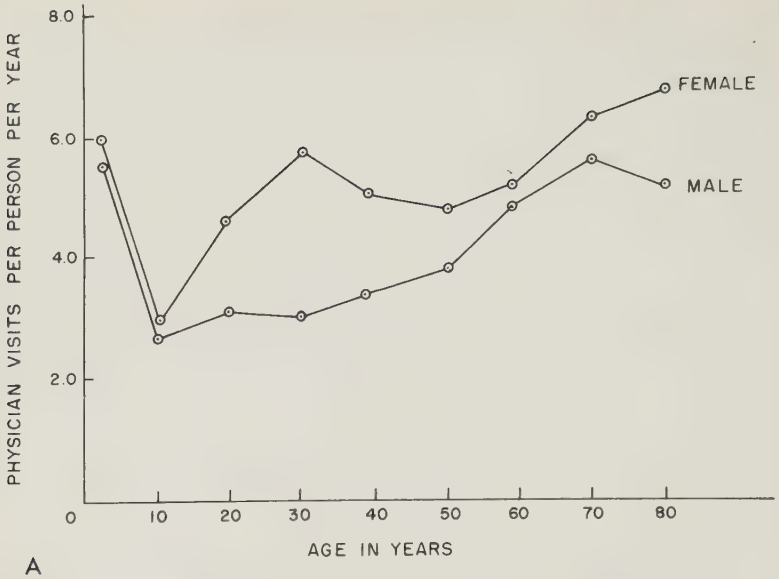

Figure 3. *A*, Number of physician visits annually by age. (Data from: National Center for Health Statistics, Series 1–49: Volume of Physician Visits July 1966–June 1967, p. 5.)

rection of volume deficits, electrolyte imbalance, and cardiac status could be expected to diminish the high mortality rate.[32] To stress the need for urgency in adequately preparing the aged patient, Lorhan's study can be compared with that of Davie et al. who found a twofold rise in mortality rate (8 vs 18.5 per cent) in patients hospitalized more than 48 hours after sustaining a hip fracture as compared to those admitted within 48 hours following fracture.[9]

PREOPERATIVE EVALUATION

Careful preoperative evaluation and preparation are essential features in managing the geriatric patient. The urgency of the contemplated surgery will of necessity influence the magnitude of the preoperative evaluation. Nevertheless, preoperative baseline evaluation of cardiac, pulmonary, renal and neurologic status is desirable to detect conditions with or without symptoms.

Medical history is the first essential and if the patient is unable to provide sufficient coherent information, every effort must be made to obtain it from family, friends, neighbors, or nursing attendants. Especially important is any recent change in mental function. Symptoms of irritability, mental confusion, and severe depression should not be dismissed summarily as being due to organic brain syndrome or "senility" without proper evaluation of cardiorespiratory function. Mental symptoms of confusion may be caused by an underlying systemic illness, especially cardiac or respiratory disease, resulting in inadequate cere-

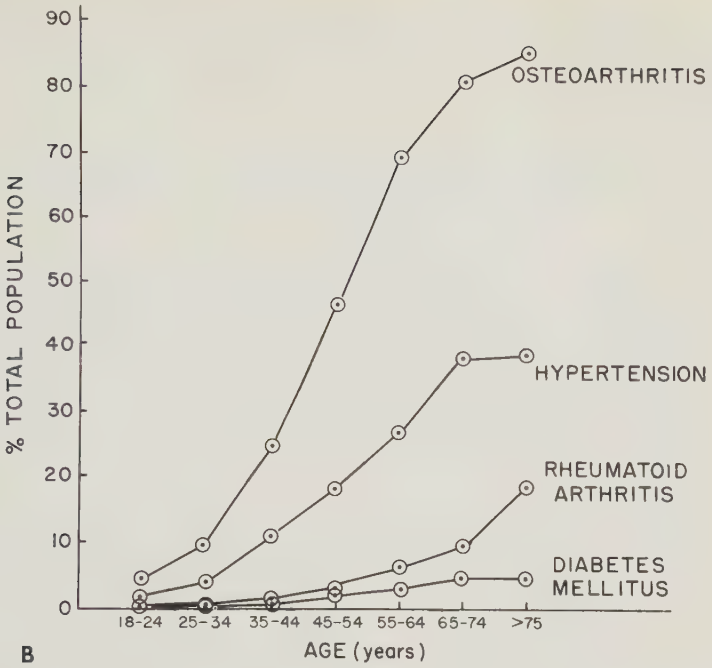

Figure 3 *Continued.* *B*, Prevalence of disease by age (Data from: National Center for Health Statistics, Series 11–2: Glucose Tolerance of Adults. United States 1960–62, p. 4 and Table 114, U.S. Bureau of the Census Statistical Abstract of the United States: 1971. 92nd ed. Washington, D.C., U.S. Government Printing Office, 1972.)

bral oxygen transport. Vitamin deficiency and electrolyte imbalance are examples of other pathologic processes which may produce a similar picture on superficial evaluation. Labeling an ill elderly patient as senile may spell the end of diagnostic or therapeutic endeavor, thereby condemning the patient to a slow death.[25] Formal evaluation of the state of consciousness should always be carried out in the geriatric patient; a specific statement written preoperatively about orientation as to time, place, and person is often useful for postoperative comparison.

Chest x-ray, electrocardiogram, complete blood count, blood urea nitrogen, and electrolyte levels should be obtained routinely. Additionally, arterial blood gases frequently provide useful information regarding the patient's pulmonary function. In lieu of a complete set of pulmonary function tests, the "match test" is a simple bedside test that may be used with a cooperative patient. A match is held 6 inches from the mouth of the patient who is asked to blow it out with his mouth wide open. Inability to do so correlates well with decreased maximal voluntary ventilation.[16]

Lewin et al., in a study of surgical patients, found that more elaborate measurements of cardiorespiratory function, including calculation of A-aDo_2 and cardiac output were helpful in preoperative assessment of the aged high risk patient. They point out the difficulty of correlating clinical findings with the degree of cardiopulmonary compensation, and

suggest that "physiologic staging" based on such measurements is a better predictor of operative mortality than the clinician's educated guess in the aged.[30]

Egbert et al. have clearly demonstrated the value of a properly conducted preoperative visit by the anesthetist.[15] Communication between any two individuals is basically by voice and sight. Unfortunately, the incidence of visual and auditory impairment rises steadily with age and therefore communication may be much more difficult. Furthermore, if any degree of organic brain syndrome is present, the visit with the geriatric patient may require more than the usual time. However, the patient should be given as much information about planned procedures as he can comfortably assimilate. The preoperative physical examination should include checking for pressure sores and if possible, placing the patient in the intended surgical position to confirm that he can tolerate such a position. In addition, the patient's head should be placed in various positions to see whether any position produces symptoms of inadequate cerebral perfusion.

The importance of maintaining proper blood volume in order to reduce overall mortality in the elderly has long been appreciated.[1] In this regard, dehydration, anemia, and hypovolemia must be considered together. On admission, a patient may be dehydrated and have a hematocrit level within normal limits. However, rehydration would result in the patient's becoming markedly anemic and requiring preoperative blood transfusion. The patient's response to a "tilt test" is a useful sign in evaluating volume status. If more than a 10 per cent increase in pulse rate or decrease in systolic blood pressure occurs when the patient sits upright for one minute, a volume deficit is most likely present. Dry mucosa, loss of tissue turgor, and oliguria are later signs of dehydration and hypovolemia.

If time permits, correction of hypovolemia should be done slowly to permit adequate adjustments by the patient's circulation. Central venous pressure and pulmonary artery catheter pressure measurements may be useful guidelines in volume replacement. Our usual clinical method of managing these patients is as follows:[36]

> If cerebral function is normal and the cardiovascular system is stable in the face of postural stress and urine output is adequate, only clearly documented losses are replaced. Alternatively, in the presence of severe hypotension, a 70 kg adult receives up to 1 liter of isotonic salt solution every 15 minutes until: vital signs are stabilized, urine output reaches 50 ml an hour, or central venous pressure rises unacceptably, or rales develop as detected by precordial or esophageal stethoscope, or total fluid volume appears unreasonable, raising the possibility of renal failure. Should any of these signs of intravascular fluid overload occur before the cardiovascular stability or urine output has been restored, fluid administration is interrupted and a positive inotropic drug (epinephrine, calcium, or digitalis) and a diuretic are given.

This method requires moment-to-moment monitoring of direct arterial and venous pressures since it is the change in pressure, rather than the absolute level, that guides therapeutic decisions.

The importance of adequate volume replacement prior to the induction of either a general or regional anesthetic must be emphasized since either can produce vasodilatation. Whether volume deficits should be

corrected preoperatively with blood, balanced salt solution, or plasma protein fraction is a matter of personal preference. It has been our custom to let the hemoglobin fall to 10 mg per ml by infusing one of the latter two solutions initially.[17]

ADMINISTRATION OF ANESTHESIA TO GERIATRIC PATIENTS

Anesthetic Requirement

Clinical experience has long suggested that an inverse relationship existed between age and anesthetic requirement. The minimum alveolar concentration (MAC) required to prevent 50 per cent of patients from responding to a surgical stimulus is a measure of required anesthetic dose. The relationship of MAC for halothane to age has been demonstrated with a decreased requirement from 1.08 per cent halothane in oxygen in the newborn to 0.64 per cent for the octogenarian.[22, 35] Although no causal relationship may exist, the decrease in anesthetic requirement with aging is associated with a decrease in cell density in the central nervous system, decreased cerebral oxygen consumption, and decreased cerebral blood flow. Bromage has demonstrated a decreased requirement for local anesthesia per epidural segment anesthetized, presumably related to a decrease in cell density.[3]

Not only is the dose required for adequate surgical anesthesia reduced in the aged, in animals, the recovery time from ether anesthesia has been shown to be markedly increased with advancing age—presumably reflecting a prolonged time for elimination of this inhalation agent by the lungs. Possible prolonged half-life of other anesthetic agents or adjuncts due to inability of the aged patient to metabolize them must be kept in mind and reduced dosages used initially until the need for larger doses has been demonstrated.[2]

Preanesthetic Medication

Preanesthetic medication refers to the use of drugs prior to the administration of an anesthetic, chiefly to decrease anxiety and provide smoother induction to, maintenance of, and emergence from anesthesia.[41] The more ill, the more elderly, the less robust, and less active the patient, the smaller the amounts of sedatives and analgesics are needed. If a patient requires analgesia for pain, this should be given. However, when a patient's grasp of reality is tenuous, one should not jeopardize that hold with a depressant or dissociative drug.[12]

Geriatric patients may be taking many drugs. Although these drugs do not fall within the definition of preanesthetic medication, specific consideration must be given to whether they should be discontinued prior to the induction of anesthesia and surgery. For example, digitalis and antihypertensive and hypoglycemic agents require specific consideration at the time premedication orders are written.

Monitoring

The pulse rate, blood pressure, and ventilation rate are monitored routinely in patients under general anesthesia. In the geriatric patient,

monitoring of electrocardiogram, central venous pressure, and temperature should always be considered and frequently done. Such additional monitoring may provide early warning of adverse trends. As adaptability to stress decreases because of limited reserve, it is especially important to avoid wide deviation in vital functions. The presence of an intra-arterial cannula to permit direct monitoring of the blood pressure and serial arterial blood gas analysis may further help in detecting adverse changes in cardiopulmonary function. One additional monitoring aid available under regional anesthesia is the ability to communicate with the patient and gauge his sensorium.

Choice of Anesthetic Technique

Formerly it was thought that general (as opposed to regional) anesthesia was fraught with hazard for the elderly patient. However, as long as adequate pulmonary ventilation and tracheobronchial toilet are provided, this need not be so. Indeed, general anesthesia may be the anesthetic of choice even if pulmonary disease is present. Such general anesthesia may represent a small amount of analgesia with a large amount of mechanical ventilation, tracheobronchial toilet, and circulatory support. Hamilton and Sokoll reported the case of a 75-year-old woman admitted 2 days after sustaining a hip fracture with near total collapse of the left lung. During general anesthesia for repair of the fracture, vigorous tracheobronchial cleansing and positive pressure inflation of the lungs produced dramatic improvement with almost complete clearing on a repeat x-ray, demonstrating the efficacy of this technique.[23]

General anesthesia involves the balanced use of several agents to provide analgesia, amnesia, sleep, muscle relaxation, and the alteration of reflexes. Many of the agents used are cardiovascular depressants that act through direct and reflex depression of myocardial activity and peripheral vascular tone. In many elderly debilitated patients, nitrous oxide inhalation may be sufficient to provide all the elements of anesthesia with minimal cardiovascular depression. Supplemental barbiturates or narcotics given as premedicants or during anesthesia may provide the necessary balance if nitrous oxide alone is not satisfactory.

If further muscle relaxation is necessary for surgical manipulation, the addition of neuromuscular blocking agents will produce this effect. Curare has been used effectively but may add the problem of vasodilatation with hypotension. Succinylcholine, a short-acting muscle relaxant, is frequently given as an intravenous drip, since it is less likely to be associated with hypotension. Pancuronium, a relatively new muscle relaxant with a duration of action similar to that of curare, has been associated with a decreased incidence of hypotension, but is sometimes associated with tachycardia.

In some patients with pulmonary disease, the possible effects of anesthesia such as decreased functional residual capacity, increased closing volume, mismatching of ventilation and perfusion, and decreased cardiac output require for safety a higher percentage of inspired oxygen than is possible with a nitrous-oxide-oxygen technique which is usually limited to 40 to 50 per cent inspired oxygen. In this case, other volatile agents, e.g., halothane, will be necessary.

One of the most common causes of malpractice action in anesthesia relates to chipping or dislodging of a decayed tooth during intubation. This is one area in which the problems are less prevalent in the aged in view of the rising incidence of edentulous patients with increasing age. Whereas less than 20 per cent of the population are edentulous at age 50, approximately 50 per cent of the patients above the age of 65 are edentulous.[16] Unfortunately, this is merely a case of trading one problem for another. Edentulous patients are notorious for being potentially more difficult in terms of airway management. We have found that leaving dentures in place is one way of overcoming this problem. Even so, the use of an endotracheal tube may be necessary. The endotracheal tube will protect the airway from aspiration and also free both hands of the anesthetist. While leaving dentures in place when patients are not intubated, we do not agree with the practice of intubating patients while dentures are in place.[45]

Regional anesthesia includes spinal (subarachnoid block), lumbar epidural, caudal epidural, and local infiltration. With spinal or epidural anesthesia a T8 sensory level will provide adequate anesthesia for lower extremity or hip surgery. Since the sympathetic blockade is usually three to four dermatomes above the sensory level, a T8 sensory level may permit retention of sufficient sympathetic response to minimize the cardiovascular depression seen more frequently with higher levels.

Subarachnoid block provides muscle relaxation, sensory block (analgesia) and retention of consciousness. Muscle relaxation may be beneficial in positioning the patient and applying traction for intraoperative maneuvers. Some elderly patients prefer consciousness for fear of losing control of what they feel may be a slim grasp of life. For the anesthetist, the ability to monitor the sensorium—watching for agitation, restlessness, or confusion—may be important in providing intraoperative care with respect to related diseases. Examples include watching for symptoms of hypoglycemia in a diabetic patient who is receiving insulin or the need for nitroglycerin in a patient with angina pectoris.

Unfortunately, the conscious state may be equally disadvantageous with a hostile, uncooperative patient who attempts to get off the table, or move the upper half of his body uncontrollably. With regional anesthesia this patient may require sedation or hypnotics to the point of general anesthesia without the benefits of formal general anesthesia, i.e., adequate ventilation and an opportunity to provide good tracheobronchial toilet. Furthermore, this sedation may be obtained with drugs that have a lingering effect after the operation, increasing the risk for the patient. For such a patient general anesthesia would obviously be preferable.

Gauthier and Hamelberg reviewed the records of 200 patients with hip fractures, half receiving spinal anesthesia and half general anesthesia, in an attempt to obtain data to support their clinical impression that spinal anesthesia was associated with lower morbidity and mortality rates. However, they were unable to find any significant difference between the two groups.[20]

The technique of performing spinal anesthesia must take into consideration the positioning of the patient, the site of the needle insertion, the baricity of the anesthetic solution, whether the continuous or single

dose technique is used, and the location where the anesthetic is to be administered (bed or operating table). Positioning of the patient will determine the baricity of the anesthetic solution to be used. Cerebrospinal fluid has a specific gravity of 1.005 ± 0.003 at 37°C. A solution of anesthetic in sterile distilled water results in a specific gravity slightly less than that of cerebrospinal fluid (hypobaric), whereas anesthetic in solution with 10 per cent dextrose or cerebrospinal fluid produces a hyperbaric solution. The hyperbaric solution will settle to the down side in a lateral position. The opposite occurs with hypobaric solutions.

By using hyperbaric solution with the patient lying in the lateral position, anesthesia of the down side can be preferentially obtained. However, the patient must be kept in the lateral position for 10 minutes to permit fixation of the anesthetic. A unilateral block (sensory) is associated with a more unilateral sympathetic block, thus permitting more sympathetic reflex compensation. A slight head-up position (achieved by blocks placed under the head of the table) should also produce a lower level of block. Caution must be taken with this maneuver for any degree of hypovolemia will be aggravated by peripheral pooling.

Single dose administration of spinal anesthesia is a very common technique. It is rapidly performed and can be done with a small gauge needle. (Spinal headache is rare in the elderly.) The single dose technique has the disadvantage of time limitation and diminished controllability of level in comparison to continuous techniques. With single dose administration of tetracaine, a 2-hour period of anesthesia may be achieved and the addition of epinephrine may prolong this to 3 hours.

Continuous spinal techniques consist of the insertion of a catheter into the subarachnoid space through a 17 gauge needle. Small doses of anesthetic solution can then be injected in increments providing more control of the level of the block.

A regional anesthetic may be administered with the patient either in bed or on the operating table. The former does provide anesthesia, making the move to the table easier if he is in pain as with a hip fracture. However, great care must be taken in monitoring the patient during the transfer.

Epidural anesthesia provides a slower onset of sympathectomy than spinal anesthesia. This allows more time to stabilize the evolving hemodynamic changes. It is, however, a more difficult block to administer and requires more drug. A caudal approach to the epidural space does diminish the chance of an accidental subarachnoid tap, but requires even more drug than the lumbar approach and is less reliable in producing anesthesia.

Field block or local infiltration may also be used especially in patients considered too decompensated for other anesthetic techniques and/or in surgical procedures which are suitable for this technique. Advantages of this technique include less fluctuation in blood pressure, more rapid ambulation, and a low rate of pulmonary complications.[48]

Blood Pressure and Tissue Perfusion

The internist's oft repeated admonition to avoid hypotension merits special comment. Target organs which might be expected to be espe-

cially sensitive to low perfusion pressures are the brain and heart. In an analysis of postoperative myocardial infarction in 365 patients with abnormal preoperative EKG's, Meaney et al. found a direct correlation between the incidence of infarction and both length of operative procedure and occurrence of intraoperative hypotension.[33] While their definition of significant hypotension (30 per cent reduction in systolic blood pressure sustained for at least 10 minutes) seems reasonable, the multiple factors influencing blood pressure make any such analysis difficult. For example, the preoperative blood pressure may be elevated abnormally due to pain and the fall following induction of anesthesia may be from an elevated pressure, rather than from a normal one. Dripps cautions against over-treatment of anesthesia-induced hypotension, since hypotension also reduces metabolic rate, produces vasodilatation, and decreases cardiac work. Aggressive treatment with pressor drugs or fluid administration may produce increased heart work, hypertension, and cerebral vascular accidents.[14]

The effect on mental function of hypotensive anesthesia in the elderly as compared to normotensive anesthesia demonstrated no appreciable difference utilizing refined psychometric tests designed to detect brain damage.[40] Again, this is a most complex area to assess with multiple factors bearing on the situation.

Nothing in this section is meant to minimize the importance of monitoring blood pressure. Perhaps the dilemma was best summarized by Dripps who stated that "the dictum should not be to treat a particular millimeter of Hg blood pressure, but to respond appropriately when tissue perfusion is judged insufficient."[14] In addition to the hazards of hypotension, anesthetists have come to fear hypertension as well since its hazards, e.g., arrhythmia, cerebral hemorrhage, and pulmonary edema, are as great as those of hypotension.

THE POSTOPERATIVE PERIOD

As with the preoperative evaluation and intraoperative management, Crile long ago stressed the importance of prevention of complications in the postoperative period.[38] Cole has emphasized that postoperative complications in the geriatric patient occur mainly in four areas: cardiovascular, hepatic, renal, and respiratory.[6] Constant attention, especially in monitoring these four areas, is essential throughout the postoperative period.

Careful attention to fluid and electrolyte balance and early mobilization of the patient further hasten convalescence and prevent many complications. Supplemental oxygen given until the patient is able to ambulate is also recommended since the decline of P_aO_2 with age has been demonstrated. It has been our practice to administer supplemental oxygen postoperatively until the P_aO_2 breathing room air is greater than 50 torr.

The anesthetist is most likely to help postoperatively in assessing the adequacy of ventilation and managing patients in respiratory failure who require mechanical ventilation. Serial measurements at the bedside

of vital capacity, minute ventilation, and inspiratory force, together with arterial blood gas measurements, are necessary to assess respiratory function adequately. Lecky and Ominsky have detailed our approach to postoperative respiratory management.[29]

One common postoperative complication which has a steadily rising incidence with advancing age is thromboembolic disease. In addition to early ambulation, other measures which may minimize the possibility of this potentially catastrophic complication include the use of support stockings, elevation of legs, and (if not otherwise contraindicated) anticoagulants.

CONCLUSION

The goal of geriatric medicine is to retain the aged in their own community as useful and productive citizens. Anesthesia and surgery can contribute to this goal by fitting the anesthetic technique and surgical procedure to the patient and not vice versa. Meticulous clinical judgment, intraoperative deliberate speed, and technical skill, combined with dedicated postoperative care, will enable many geriatric patients to live longer, more healthy lives. In view of the increasing numbers of geriatric patients appearing on operating room lists, their unique features must be appreciated by all concerned in order to insure optimal care.

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Deliberate Hypotension

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Deliberately lowering the blood pressure during surgery can reduce blood loss, provide a drier field, make dissection easier, reduce the occurrence of hematomas, and speed up surgery.

In this article we intend to discuss the indications for induced hypotension, its risks, the assessment of patients, and techniques for intraoperative and postoperative management.

INDICATIONS

There are three broad groups of indications for lowering the blood pressure: first, to protect the patient from hemorrhage which might make the operation impossible or destroy its results; second, to avoid massive hemorrhage; and third, to treat hypertension and avoid its consequences. Action may be required at any time during the perioperative period.

A few operations are very difficult without hypotension. In middle ear surgery even slight hemorrhage will sometimes lead to fibrosis and obliteration of the surgical result. Vascular tumors of the central nervous system and aneurysms of the cerebral vessels can be attacked more quickly and more precisely in a relatively bloodless field.

Hypotension will reduce major blood loss in prostate and bladder surgery, correction of aortic coarctation, radical pelvic surgery, and some orthopedic procedures. In radical head and neck surgery, especially for vascular tumors, less blood is lost and careful dissection can be made more easily in the drier field. Blood loss during portacaval shunting can be reduced from 3200 to 1300 ml on the average.[7]

Alarming hypertension often occurs during induction of anesthesia and in the postoperative recovery room; it is especially troublesome in untreated hypertensive patients. Arrhythmia and EKG changes of myocardial ischemia are common.[8, 22] Every anesthesiologist should be prepared to treat hypertension in such circumstances.

RISKS

In an earlier time hypotension was usually a sign of overdosage with ether or cyclopropane. Since the advent of halothane, anesthetists have come to accept a slight drop in pressure as one sign of adequate anesthetic depth. If a further drop

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in pressure can be beneficial in some respects, what limits should one set? We can try to assess the risks by attempting to answer two questions: first, what are the overall risks of induced hypotension? Second, what are the acceptable limits of hypotension for each organ system?

Overall Morbidity and Mortality

One of the more damaging indictments of controlled hypotension was contained in the articles by Hampton and Little,[12, 13, 18] who queried anesthetists in the United States, Great Britain, and Ireland, and reported the complications in 27,930 cases. The overall rate of complications was 1 in 31 cases, with a death rate of 1 in 291, 1 in 417 probably related to anesthesia and hypotension. The more common nonfatal complications were "reactionary" hemorrhage, delayed awakening, blurred vision, and anuria or oliguria. A survey of the cases reported in 1958–1963[17] revealed 113 deaths in 13,264 cases (1 in 117). Interestingly, only 3 per cent occurred during operations. One wonders if better postoperative care would not have prevented some of the other 97 per cent. There were no good data in these studies on the level of blood pressure achieved or the length of hypotension, and no more recent large series are available. Recent advances include wider use of the short-acting drugs trimethaphan camsylate (Arfonad) and sodium nitroprusside. These drugs have been available for a good many years, but were used in less than 1.8 per cent of Little's series. The drugs commonly used before 1953 were pentamethonium and hexamethonium, which are rather long-acting compounds. We believe that the short-acting drugs, especially nitroprusside, are safer because of their very transient effects. Better monitoring techniques now available are likely to make hypotension more controllable and therefore safer. Intra-arterial pressure monitoring, central venous pressure monitoring, and arterial blood gas measurements are all developments which have become widely available in recent years. Both morbidity and mortality are probably lower today than in 1953.

It is worthwhile attempting to compare the risks of induced hypotension to the risks of blood transfusion. In a survey of hepatitis following cardiac surgery, the incidence of complications varied greatly depending upon the number of transfusions and the characteristics of the donor population.[9] Morbidity, defined as symptomatic hepatitis, ranged from 0 to 1.56 per 100 units of blood, i.e., from nil to 1 in 66 transfusions. Since most patients received more than 1 unit of blood (mean 7.7), the incidence of hepatitis was from 0 to 8.6 per 100 patients or as high as 1 in 12. This is thus higher than the complication rate of 1 in 31 reported for induced hypotension. Mortality in the hepatitis study was about 1 in 7700 transfusions or 1 in 1000 patients, probably significantly less than the mortality of 1 in 417 related to anesthesia and induced hypotension.

The incidence of hepatitis today is probably less than that reported in 1972, because most of that study predated the screening of donor blood for hepatitis antigen. Other complications of transfusion are the common but usually minor allergic reactions, and the rare but serious blood group mismatches, which are usually due to clerical error. Two advantages of hypotension which cannot be quantified are the ability to save blood when the supply is limited, and the ability to increase the ease of operation. It is probably reasonable to conclude that hypotension may cause nearly as much morbidity as transfusion, and even more mortality.

Central Nervous System

One of the principal dangers of induced hypotension is hypoxic damage to the brain. The normal balance between cerebral metabolic usage of oxygen ($CMRO_2$) and the supply of oxygen is upset by hypotension and anesthesia. Cerebral blood flow (CBF) is normally regulated through a fairly wide range of arterial blood pressure. However, extremely low blood pressures or increases in intracranial pressure may drop the perfusing pressure enough to reduce CBF. What is a safe value for systolic or mean blood pressure—one that will cause no significant decrease in cerebral function in anesthetized man? This is not an easy question to answer because of the difficulties in measuring cerebral function, espe-

cially during anesthesia, and the significant risk in performing experiments of this nature on man.

Central nervous system complications were the most frequent of all complications in the survey of Hampton and Little.[12, 13, 18] Delayed awakening, blurred vision, retinal or cerebral thrombosis occurred in 1.3 per cent of their 27,930 cases. However, none of these complications occurred in patients whose systolic pressure was kept above 80 torr. Thus, 80 torr is probably a very safe lower limit for healthy, normotensive patients. Is there any evidence from either experimental or clinical studies that pressures lower than 80 systolic can be reached safely? Are there special types of drugs or monitoring procedures which will make hypotension safer? In experimental situations regional cerebral blood flow measurements, the Po_2 or lactate concentration in jugular venous blood, or spectrophotometric measurements of the brain surface may give some indication of brain hypoxia. Electroencephalographic slowing and decreased voltage are seen when hypoxic damage has occurred. But there is no convenient and accurate method of measuring the adequacy of cerebral oxygenation under clinical conditions in man. A number of anesthetic agents decrease the cerebral metabolic rate, but there is not a particularly good correlation between depth of anesthesia and depression of metabolism except for enflurane, which interestingly decreases both $CMRO_2$ and cerebral vascular resistance.[14]

In conscious subjects signs of cerebral hypoxia appear when jugular bulb oxygen saturation is less than 30 per cent (Po_2 about 20 torr), or when mean arterial pressure is less than 55 torr, or when CBF is less than about 31 ml. $min.^{-1}$ 100 gm^{-1}. In subjects anesthetized with halothane and tilted 25° head up, the jugular bulb Po_2 was normal (35 torr) at systolic blood pressures of below 50 torr in some subjects.[5]

In another study psychologic tests were administered (to healthy young subjects) before and after anesthesia. No difference could be shown between the subjects who were kept at normal pressures and those who were made hypotensive to systolic pressures of 40 to 80 torr (mean 63) for an average of 50 minutes.[4]

A recent article reviewed evidence for the limits or pressure tolerance in hypotensive anesthesia.[14] Patients who are hypertensive develop signs of cerebral hypoxia at higher pressures than do normal patients. The hypertensives tend to have persistently high cerebral vascular resistance and, therefore, the cerebral blood flow drops to a critical level of about 30 $ml \cdot min^{-1} \cdot 100\ gm^{-1}$ at a mean arterial pressure higher than that for normals. For example patients who had a mean arterial pressure of 180 torr gave evidence of cerebral hypoxia at mean arterial pressures of 90 torr. Extreme hyperventilation may reduce cerebral blood flow and should be avoided. The recommendations of Harp and Wollman[14] seem reasonable: a cerebral perfusion pressure above 50 torr is probably adequate in normal individuals. Patients with hypertension or cerebral vascular disease are less likely to tolerate hypotension and since the practical monitoring methods are relatively crude and unreliable, induced hypotension should not be used with these patients.

The Heart

Hypotension makes it more difficult for the heart to obtain oxygen, but it also reduces the amount of cardiac work. Myocardial work is reduced when either cardiac output or mean arterial pressure are reduced. However, decreased coronary blood flow may result either from decreased pressure during diastole or from decreased length of diastole if tachycardia is present. What is the net effect of these conflicting processes?

In the two large series of hypotensive anesthetics, about 32 complications and two fatalities occurred in every 1000 cases. However, in another report electrocardiographic evidence of ischemia was found in 40 per cent of hypotensive patients, but none of these developed permanent changes.[23]

The normal coronary circulation can apparently decrease its resistance as needed to maintain normal blood flow and oxygenation in spite of reduced perfusion pressure. The situation is quite different in stenotic coronary arteries. One can view the resistance of the stenotic section as being in series with the resistances of the myocardial vessels downstream from it. Flow through such an area

of myocardium is inversely proportional to the sum of the resistances: (flow) = (perfusing pressure) ÷ (resistance of stenotic section plus resistance of myocardial vessels). Thus a fall in perfusing pressure will decrease the flow unless the resistance of myocardial vessels decreases, which it normally does with autoregulation. But if the resistance of the stenotic section is fixed and high with respect to the other resistance, then the resistance of the stenotic section is the limiting factor and flow will decrease in proportion to decreasing pressure.

There are few studies of myocardial blood flow during induced hypotension, but one study of hypertensive patients showed that coronary blood flow was reduced by spinal anesthesia as much as 50 per cent. However, myocardial work and oxygen consumption decreased proportionally so that there was no evidence of myocardial ischemia.[11]

Induced hypotension has even been shown to improve myocardial performance in certain patients with refractory heart failure. In a small series of patients with ischemic heart disease or cardiomyopathy, the infusion of sodium nitroprusside decreased the blood pressure but also increased cardiac output, slowed the heart rate, increased the stroke volume and the ejection fraction, and decreased left ventricular filling pressure. The mechanism is uncertain, but probably the improvement resulted from decreased peripheral resistance decreasing the afterload, allowing the weakened myocardium to eject blood more efficiently and at less oxygen cost.[10]

In summary, both coronary flow and myocardial oxygen demand decrease in normal subjects with decreasing blood pressure, tending to make a moderate amount of hypotension harmless. Patients with coronary artery stenosis may require higher perfusing pressures and so are more likely to be harmed by hypotension. Definite limits to the hypotension cannot be set, but electrocardiographic monitoring will usually show ischemia before permanent damage occurs.

The Lungs

There are probably no specific complications of hypotensive anesthesia involving the lungs. However, the studies of Eckenhoff and colleagues[4, 6] showed that physiologic deadspace, as calculated by the Bohr equation, increased an average of 60 ml during hypotension with head-up tilt. The ratio of deadspace to tidal volume, V_D/V_T, increased from 0.32 to 0.45; V_D/V_T as high as 0.92 was reported. Deadspace also increased in patients who were placed in a head-up position without being made hypotensive. Though no measurements of pulmonary artery pressure were made, the likely explanation of this finding is that a fall in pulmonary artery pressure causes poor perfusion of the lung apices, resulting in an apparently increased deadspace, or more "Zone I." The practical consequence is that it is necessary to ventilate these patients with higher minute volumes than if they were supine and normotensive. Since the increase in deadspace leads to a larger difference between arterial and end-tidal P_{CO_2}, the end-tidal measurement is not particularly reliable as an estimate of arterial P_{CO_2}. Therefore, arterial blood gas tensions should be measured during most procedures.

Splanchnic Blood Flow

Blood flow through the liver is easily decreased by increased sympathetic stimulation, as occurs with some anesthetics and with hemorrhage. In theory, at least, agents which cause vasodilation may tend to diminish the decrease in splanchnic blood flow. For example, hemorrhagic hypotension in dogs produces liver damage which is prevented by vasodilation with dibenamine. Many anesthetic agents decrease splanchnic blood flow either by decreasing blood pressure, or by increasing sympathetic activity which increases splanchnic vascular resistance. They also decrease splanchnic blood flow more than they decrease splanchnic oxygen consumption.[20] The effect of induced hypotension on splanchnic blood flow has apparently not been studied, but vasodilating agents such as nitroprusside or ganglionic blockers would theoretically diminish the drop in flow usually associated with decreased blood pressure. On the other hand, induced hypotension has been shown to reduce blood loss during portacaval shunting;[7] it hardly seems likely that this would occur if portal flow were not decreased. In summary, the situation is unclear.

The Kidney

Anesthetics usually decrease urine output. This is sometimes associated with stimulation of antidiuretic hormone secretion and sometimes with decreased renal blood flow, due either to sympathetic stimulation or hypotension. Some of the renal blood flow may be restored toward normal by ganglionic blockade. Not much has been written concerning renal blood flow and urine output during hypotensive anesthesia. Renal complications have been variable. Enderby recorded none in 9107 cases. In contrast, Hampton and Little reported 54 cases of anuria and 30 cases of oliguria in their series of 21,125. There were eight deaths associated with renal failure. None of the patients with systolic pressures maintained above 80 torr developed anuria. There are still many unknowns, including the effect of different hypotensive agents on renal blood flow and urine output and the effects of these agents and anesthetics on distribution of blood flow between cortical and medullary areas of the kidney.[20]

Reactionary Hemorrhage

Reactionary hemorrhage is bleeding in the wound within 24 hours of surgery. It may be due to a disorder of coagulation, but is more likely due to inadequate hemostasis at the time of operation. A small vessel severed during hypotension may not bleed until the blood pressure is elevated. If the pressure is held low until the skin is closed, a subsequent increase in pressure may induce hemorrhage, the effects of which include wound hematoma encouraging infection, tracheal compression and ventilatory arrest after neck surgery, and massive blood loss. Reactionary hemorrhage is often not seen until several hours into the postoperative period. It may be triggered by coughing, presumably dislodging a thrombus, or by a hypertensive response to stress, such as pain or a full bladder. The anesthesiologist and surgeon must be aware of the danger of reactionary hemorrhage and arrange for a pressure increase before wound closure in an attempt to reveal any potential sources of bleeding.

PREOPERATIVE ASSESSMENT

The history and system review should give clues as to the relative safety of hypotension. Frail, debilitated patients will usually tolerate less blood loss and require smaller doses of vasodilators and anesthetics than robust patients. Dehydration or blood loss should be corrected before anesthesia is induced. Central nervous system deficits must be noted to give an accurate baseline for postoperative examination. Cerebral vascular disease is a relative contraindication to hypertension. Hypertension is also a contraindication to induced hypotension, but should alert the anesthesiologist to the likelihood of acute hypertension occurring during induction or recovery. Ischemic heart disease probably contraindicates profound hypotension and makes careful monitoring of the electrocardiogram essential, but does not contraindicate moderate hypotension. Angina may be brought on by acute hypertension which may occur intraoperatively. Previous myocardial infarction is likely to mean a reduced ability to tolerate anesthesia or hemorrhage. Cardiac failure should be treated preoperatively, but again probably does not contraindicate slight hypotension. Reduction of the cardiac afterload may even be beneficial.

If hypoxemia is present, it may be exaggerated by ventilation-perfusion abnormalities intraoperatively. Carbon dioxide retention is likely to be made worse by the increased physiological deadspace or V_D/V_T during hypotension, and ventilation should be increased accordingly. Hepatic function may possibly be diminished by hypotension, though the evidence is not clear. The existence of hepatic insufficiency should probably be regarded as a relative contraindication, and baseline liver function tests should be obtained.

Laboratory tests should include hemoglobin, hematocrit, urinalysis, EKG, and chest x-ray, serum urea, and glucose. Additional tests which may be indicated are serum electrolytes, bilirubin, transaminases, arterial blood gases, exercise EKG, and serum creatinine. Several measurements of blood pressure should be made

preoperatively to provide an adequate baseline. Blood should be typed and crossmatched as necessary and human albumin or plasma protein fraction should be available.

TECHNIQUES FOR PRODUCING HYPOTENSION

The anesthesiologist should have a definite plan, taking into account the site of operation, when and for how long hypotension will be necessary, posture and the possibility of changing it, and the patient's peculiarities. For example, in ear surgery the preparation takes a short time and hypotension must be induced within 10 minutes or so; in total hip replacement positioning and skin preparation and draping may take 45 minutes, allowing a more leisurely titration of the blood pressure. In hip surgery it is usually sufficient to keep the pressure at 80 or 90 systolic from opening to closing; in cerebral aneurysm surgery it may be better to keep the pressure at a more normal level until the aneurysm is nearly isolated, then drop it to a profoundly low level for a few minutes.

Almost every conceivable combination of agents has been used at one time or another. It is probably best to use one or two basic techniques at first until one gains familiarity with the problems peculiar to induced hypotension. A technique we often use is to establish an adequate depth of anesthesia with nitrous oxide, oxygen, and halothane (about 1 per cent) or enflurane (about 1.5 to 2 per cent) and then add sodium nitroprusside, trimethaphan, or pentolinium to achieve hypotension. This combination allows fairly quick changes in anesthetic depth by varying the concentration of inhalational agent, an important consideration when a long-acting drug like pentolinium is used.

Agents

The agents used for inducing hypotension can be classified by their sites of action:

Sympathetic Ganglionic Blockade. Hexamethonium ("C6" and related compounds have been used both for treatment of hypertensive emergencies and for induction of hypotension. Pentolinium (Ansolysen) and trimethaphan camsylate (Arfonad) act in a similar fashion, although the latter has a direct dilating effect on vascular muscle as well. They are usually used as shown in Table 1. Hexamethonium and pentolinium have largely been replaced by trimethaphan, which offers the advantage of continuous administration and fairly transient action. Trimethaphan's decay of action takes longer than its onset, however, and often provides a challenge in the postoperative recovery phase. Tachyphylaxis and resistance to this drug's action has been a regular feature of its use. Its side effects are many and occasionally bothersome, especially histamine release. It may potentiate curare, an effect which is not reversible by neostigmine. It is broken down by plasma cholinesterase and thus may have a prolonged action in patients whose cholinesterase is deficient or inhibited.

Central Nervous System Depression. Chlorpromazine probably acts at several levels within the central nervous system, including the hypothalamus and brain stem. It is uncertain whether its hypotensive effect is due more to this

Table 1. *Dosage and Duration of Effect of Agents for Inducing Hypotension*

DRUG	USUAL ADULT INTRAVENOUS DOSE	APPROXIMATE DURATION
Hexamethonium	25 to 300 mg	1 hr (4 to 8 hrs)
Pentolinium	2 to 20 mg	45 min (4 to 8 hrs)
Trimethaphan	1 to 4 mg per min	5 to 30 min
Nitroprusside	15 to 800 μg per min	2 to 5 min

or to its α-adrenergic blocking action. Hypotension induced by chlorpromazine can be reversed by calcium.[16]

Blockade at α-Adrenergic Receptors. Chlorpromazine has some α-blocking activity in vivo: it is unclear how its hypotensive effect is mediated in vitro. Its duration of action is almost 24 hours. Other α-blockers have not been used much to induce hypotension.

Direct Inhibition or Relaxation of Vascular Smooth Muscle. Sodium nitroprusside is an extremely useful agent because of its rapid onset and decay and its lack of serious side effects. It is infused intravenously in a concentration of 100 μg per ml at a rate of about 100 (15 to 800) μg per min, preferably with a syringe or roller pump with repeatable, finely graduated settings. Side effects of large doses include thiocyanate toxicity in patients with hypothyroidism or renal insufficiency, and an undetermined, but probably remote, risk of cyanide poisoning.[1, 19, 24, 25]

Diazoxide is a new intravenous antihypertensive agent which produces a prompt fall to normotensive levels in most patients. Its use to produce deliberate hypotension has not been reported, but it is effective in treating postoperative hypertension.

Decrease in Cardiac Force (Inotropy). Propranolol can be used in combination with other drugs to decrease the force of cardiac action or to diminish the tachycardia which often occurs reflexly when hypotension is induced with other agents.[15] Complications include bronchoconstriction, hypoglycemia, cardiac failure, and intractable hypotension. Halothane produces several different effects. There is apparently some depression of vascular smooth muscle, but sympathetic outflow and total peripheral resistance may actually increase.[16] The cardiac output, stroke volume, and various indices of myocardial contractility are depressed; this is probably the main cause of hypotension. It is not yet established whether this is an advantage or a disadvantage.[21]

Monitoring During Operation

Blood Pressure. It is obviously important to be able to measure arterial pressure reliably and accurately. The Korotkoff sounds are not very reliable at low pressures, so we would recommend one of three other methods. An intra-arterial cannula connected to an electronic transducer or anaeroid gauge has the great advantage of instantaneous readout, requiring no effort at the time of measurement when hands may be busy with other tasks. It requires a little extra time and equipment and a risk of slight morbidity. Usually the radial artery is the most convenient to use, but before cannulating it the anesthesiologist must be certain that ulnar flow is adequate by performing Allen's test. The second method is the use of a cuff with a Doppler ultrasonic pulse detector at either the radial or brachial artery. This is quite sensitive and noninvasive, but requires inflation of the cuff and is very dependent on positioning. The third method, the oscillotonometer, is the choice of many experienced anesthesiologists who value it for its ease, simplicity, economy, sensitivity, and lack of morbidity. We encourage residents to select monitoring appropriate for the degree of hypotension and the abruptness of pressure drop likely to be aimed for. For example, systemic arterial systolic pressures of 80 to 90 torr will give an adequately dry field in many procedures; these may be monitored frequently and noninvasively with the oscillotonometer. In contrast, the hypotension induced for surgery of an intracranial aneurysm must be profound, often of rapid onset and sometimes induced more than once during a procedure; it should certainly be monitored by direct arterial cannulation.

Blood Loss. When hypotension is induced during procedures where more than a few hundred milliliters of blood will be lost, an accurate estimate of loss must be made. The hypotensive patient cannot compensate well for hypovolemia and normal blood volume must be maintained. Therefore, sponges should be weighed and graduated suction bottles should be used. Blood loss should be replaced by blood or plasma protein fraction in most cases. The anesthesiologist should also observe the operative field to determine what pressure seems to be necessary to diminish the rate of bleeding. He should communicate freely with the surgeon to estimate the degree of bleeding and the adequacy of the "dry field."

Respiration. One has to assure a clear airway and adequate gas exchange. So unless there is some specific contraindication, one should intubate the trachea and assist or control ventilation. Large tidal volumes—about 10 or 12 ml per kg at a rate of 9 or 10 breaths per min—will give 90 to 120 ml per kg min and should be sufficient as a starting point. Increased deadspace, particularly in the head-up position, may necessitate even greater ventilatory volumes. In most procedures the arterial blood gas tensions should be measured to prove the adequacy of oxygenation, to avoid hyper- or hypoventilation, and to detect metabolic acidosis. Metabolic acidosis may be the earliest clue to inadequate tissue oxygenation.

Central Nervous System Function. The electroencephalogram is the only electromechanical monitor available. Either bifrontal or fronto-occipital leads are useful. Slowing, decreased amplitude, or seizure activity may indicate cerebral ischemia, but these are late signs. Some operators like to use the respiratory pattern as an index of surgical approach to vital brain stem centers. If this seems to be necessary, respiration should be assisted to insure adequate gas exchange. Pupillary size and reaction to light should be followed.

Heart. The pulse should be felt; its fullness is related to vasoconstriction, stroke volume, and blood pressure. But it is not quantitative and is useless as a basis for critical decisions. Displays of various pulse monitors are little better. The electrocardiogram should always be used to look for arrhythmias and myocardial ischemia. The classical signs of myocardial ischemia are ST segment depression and T wave inversion. These and many other changes can occur during hypotensive anesthesia. The other changes: P wave axis shifts, QRS axis and vector changes, QT_c change, T wave axis changes, ST deviation, nodal rhythm, and sinus tachycardia have all been reported, but their significance is uncertain and they usually revert to the preoperative pattern after operation.[23] The simultaneous occurrence of ST depression and T wave inversion should probably lead one to correct hypotension if the surgical situation permits, but there is no direct proof that this is necessary. T wave inversions should be diagnosable on any operating room monitor scope; ST changes require a low frequency response which is not available on some monitors.

The central venous pressure or pulmonary capillary wedge pressure should be measured when heart failure or massive hidden blood loss are likely to be encountered. Otherwise, blood and fluid replacement can be made on the basis of observed blood loss. Propranolol or deep halothane may raise central venous pressure, but concurrent use of ganglion blockers or sodium nitroprusside may reverse this change. Measurement of cardiac output is usually confined to research applications.

Induction and Maintenance of Anesthesia

A secure intravenous infusion is mandatory, appropriate for the expected blood loss: one or two 14 to 18 gauge plastic cannulae are generally necessary. Electrocardiographic leads and blood pressure cuff should be attached. If there is to be continuous monitoring of the intra-arterial blood pressure, the cannula may be placed preoperatively, allowing the anesthesiologist to see rapid changes in pressure during induction of anesthesia and to induce hypotension soon after anesthesia.

The induction should be smooth to minimize hypertension, coughing, tachycardia, and venous engorgement. The trachea should be anesthetized topically before intubation to prevent reflex tachycardia and hypertension. A typical sequence might be: d-tubocurarine (3 mg), oxygen, thiopental, succinylcholine, laryngotracheal spray, intubation, maintenance with 1 per cent halothane, 60 per cent N_2O, 40 per cent O_2, and d-tubocurarine, if needed. Ventilation should be assisted or controlled.

It is convenient and safe to have a separate intravenous infusion if trimethaphan or nitroprusside is to be used, so that no drug will be trapped in the deadspace of the intravenous tubing and perhaps washed in when least desired.

The patient's posture may be dictated either by the nature of the operation or by the need to induce venous pooling in the legs and reduce venous engorgement in the upper part of the body. Posture and positive pressure ventilation are

usually easy to reverse and will give some idea of how labile the patient's circulation will be.

Ideally, the anesthesiologist should take adequate time titrating the pressure to the desired level. After the patient has been positioned and a stable level of anesthesia achieved, the hypotensive agent should be started. If sodium nitroprusside is to be used, it is infused very slowly, (say 10 μg per min) the dose doubled about every 2 minutes when it is clear that the effect is inadequate. Ultimately, the required degree of hypotension and rate of infusion will depend on inspection of the wound and the compromise between hemostasis and safe perfusing pressure.

Alternatively, giving the test dose as a bolus rather than an infusion allows one to see the magnitude *and* time course for the effect of a precisely known amount of drug. It is then relatively simple to pick a starting rate of infusion. If sodium nitroprusside is to be used, 20 to 50 μg is administered; even less should be used in small or old patients. If this produces a drop to the desired level, lasting 1 or 2 minutes, infusion is begun at an appropriate rate. If the test dose is insufficient, it is increased 50 or 100 per cent until a dose is reached which produces the desired effect. For example, if 50 μg produces a fall of pressure to 80 systolic lasting for 2 min, the initial infusion is set at 25 μg per min. The blood pressure is of course observed very closely and the infusion rate regulated as necessary. Continuous intra-arterial pressure monitoring makes control of these trends easier.

Trimethaphan can be used in much the same way but the circulatory changes take longer to commence and tend to overshoot more. We feel that if a short acting drug is to be used, nitroprusside is superior, and we prefer pentolinium as our longer-acting drug.

If pentolinium is to be used, the average dose should be about 50 μg per kg. Usually we give 1 or 2 mg, repeated after 10 minutes, then perhaps again. Its effect lasts 2 to 4 hours, so beware of postoperative hypotension! Good nursing care in the recovery room and on the ward is especially important because postural hypotension and reactionary hemorrhage may occur several hours later.

Troublesome tachycardia can be controlled by small doses (0.5 to 1 mg) of propranolol, which also reduces the dose of ganglion blocker or nitroprusside necessary.

It is essential to maintain adequate replacement of shed blood, using blood or a plasma substitute. The patient during induced hypotension cannot compensate for blood loss by vasoconstriction, and tachycardia is undesirable.

The anesthesiologist should be able to increase or decrease the degree of hypotension as necessary to control bleeding or to expose bleeders during closure. The pressure can be raised by stopping the infusion or by giving a pressor such as phenylephrine or methoxamine.

Postoperative Care

Ninety-seven per cent of the deaths attributed to hypotensive anesthesia occurred in the postoperative period. While some of these were delayed deaths following intraoperative insults, many others were due to "accidents" in the recovery phase—obviously a dangerous and neglected period. Close care has to continue until the effects of the anesthetics and hypotensive agents have worn off.

Good postoperative care begins with assessing the patient's ability to ventilate adequately and maintain a patent airway before the anesthesiologist leaves him. If in doubt, one should measure minute volume and inspiratory and expiratory forces, and use a nerve stimulator to assess the reversal of curare. There is an argument for extubating the trachea before the patient awakens: coughing and retching may provoke bleeding after head and neck or ear surgery.

Sudden movement should be avoided: the patient should be moved gently and carefully from operating room table to recovery room bed. Sudden lying down or elevation of the feet may increase venous return and cause right heart dilatation. Lowering the feet may diminish venous return enough to cause severe hypotension. The patient should be taken to the recovery room and his vital signs should be measured at least every 5 minutes until they are stable. Supplemental

oxygen should be used: the patient is probably unable to compensate for hypoxia by increasing his cardiac output; having extra inspired oxygen provides an extra margin of safety. The patient should lie flat for 4 or more hours if a long-lasting agent such as pentolinium was used, and then sit or stand slowly only with an attendant present. The operative site should be observed closely for the first 24 hours to detect reactionary hemorrhage.

Respiratory insufficiency can be caused by any of the usual problems: inadequate reversal of relaxant, residual anesthetic, bleeding into the pharynx, laryngospasm. After neck surgery the airway may be compromised by hematoma, edema, or damage to the larynx.

Patients should be given narcotics judiciously. The blood pressure may continue to be unstable for several hours after hexamethonium or pentolinium, or for 24 hours after guanethidine or chlorpromazine.

SUMMARY

Deliberate hypotension can reduce major blood loss and in delicate operations can produce a drier field increasing the ease of surgery and the likelihood of a good result. The techniques used to induce hypotension can also be used to avoid dangerous hypertension during and after surgery. These benefits must be weighed against the risks of inadequate perfusion: especially cerebral, myocardial, or renal. In previously normotensive patients these risks are minimal when the arterial pressure is held above 80 torr systolic, and may be acceptably small even at mean pressure of 50 to 60 torr. Previously hypertensive patients show signs of cerebral ischemia at higher pressures; they should probably not be subjected to deliberate hypotension, but they also can be harmed by severe hypertension which can be avoided by the proper use of hypotensive agents.

For most situations a balanced technique is suitable: after a stable anesthetic level has been achieved using halothane or enflurane, hypotension can be induced with sodium nitroprusside or trimethaphan camsylate. Longer-acting agents such as pentolinium are sometimes desirable, but the shorter-acting agents are easier to control. Careful monitoring with observation of intra-arterial pressure, electroencephalogram, electrocardiogram, and determination of arterial blood gas tensions is likely to make for safer conduct. Close postoperative observation is essential.

With careful preparation and monitoring deliberate hypotension can be a safe technique for reducing blood loss or facilitating delicate procedures.

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Physical Hazards in the Operating Room

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The physical hazards of the operating room fall into two major categories: those arising from electrical sources, and those arising from combustion processes. The purpose of this article is to review some of the physical principles relating to electrical injuries, fires, and explosions. An understanding of these physical principles is necessary for the development of rational programs for their control.

ELECTRICAL HAZARDS

The incidence of electrical injuries has increased in the past two decades because of an increase in the number of electrical devices currently used in medical care and, especially, in the operating room. Electrical devices fall into three categories: (1) labor-saving devices, e.g., electric tables, dermatomes, drills, saws, etc.; (2) energy-conversion devices, such as hypothermia units, blood warmers, heat exchangers, transducers, electrosurgical units, etc.; and (3) information display devices, cathode ray oscilloscopes, meters, x-ray machines, etc.

All electrical accidents result from the flow of current through an inappropriate pathway. The type of injury that occurs, whether it be ventricular fibrillation or a burn, is determined by two factors: the site of the current flow, and the current density. Current density is the ratio of the total current flow to cross-sectional area available for conduction. For any given amount of current, the current density will increase in inverse proportion to the area of the available conducting pathway.

For current to flow through the body, there must be a difference of electrical potential between two points. The operating room and intensive care unit establish conditions which are favorable for this occurrence because patients are simultaneously connected to several electrical devices. The patient and/or personnel in the area have many opportunities for making a good ground connection through body contact with instrument cases, bed frames, and plumbing. If, at the same

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time, they come in contact with a source of electrical potential from some faulty device, current will pass between those two points.

Power distribution systems of most operating rooms utilize an isolation transformer. The isolation transformer allows current to flow only between the secondary leads of the transformer, but not between any one of the transformer leads and ground (isolation means isolation from ground). Thus, if patient or personnel are in contact with ground and with one of the leads of the secondary transformer, an electrical circuit is *not* completed and, therefore, no current flows through the individual. An additional feature of the isolation transformer is the provision of an alarm system. Any faulty electrical device which allows one of the secondary leads to come in contact with ground, as might be caused by broken insulation or improper wiring, trips an alarm. The offending piece of equipment can thus be removed before an accident occurs. It is important to realize, however, that isolation transformers do not protect patients from microshocks due to leakage currents.

Leakage Current

Electrical devices normally have a small leakage current. Leakage currents develop from sources of alternating current in the device which radiate energy to other parts of the device or circuit. This stray current is conducted to ground via the ground wire of the instrument and is small (microamperes). Leakage current may increase with faulty insulation, component failure or deterioration, or improper hook-up to the power receptacle (via an improperly wired receptacle, a cheater plug, or an extension cord). The National Fire Protection Association has developed safety standards for electrical power distribution systems and electrical devices used in patient care.[3] The standards are defined for patients grouped into classes of electrical shock susceptibility ("Risk Categories"). The maximum leakage current specified for a single device for use with a critically ill patient with centrally placed catheters or electrodes (Risk Category III) is 10 microamperes.

Electrocution or Shock Hazards

Ventricular fibrillation or ventricular standstill will occur with aberrant current flow through the myocardium if the current density through the myocardium is sufficiently great to reach its fibrillating threshold. Roy[6] has demonstrated this relationship in dogs using catheter electrodes of different cross-sectional area. Roy has defined two conditions, the first is "pump failure," occurring when the current density is sufficient to cause cardiac standstill, sinus rhythm returning spontaneously when the current flow is interrupted. His second end point is ventricular fibrillation which is not spontaneously reversible. It is important to note that pump failure occurs at lower levels of current density than does ventricular fibrillation. Pump failure may represent the more likely hazard due to the combined leakage currents of several electrical devices attached to the highly monitored patient. These minute currents which are below the level of perception are called microshocks and they represent a significant life threat to patients with cen-

trally placed catheter systems or endocardial electrodes. In a macroshock, a large readily perceivable flow of current occurs between two points on the body. Whether micro or macro, if the current density, as a result of this current flow, is sufficiently high through the myocardium, ventricular fibrillation will occur. Electrical safety programs are designed to minimize the possibility of this occurring.

Electrical Safety Programs

One of the most effective means for reducing electrical accidents is an electrical safety program encompassing preventive maintenance, calibration of electrical equipment used in patient care, and the education of personnel. Such programs have been detailed by Noble.[4] The essence of these programs includes surveys and maintenance of the power distribution system (receptacles, isolation transformers, alarms, ground faults, detectors) and equipment control programs. Equipment control programs require a tightly controlled equipment inventory and regularly scheduled maintenance and inspection including calibration of the devices. These programs must allow for inspection of newly purchased equipment, or recently repaired equipment, to insure that the manufacturer's and/or the hospital's electrical safety standards are met.

Although well recognized as an important aspect of safety in industrial settings, safety education in hospitals is generally a haphazard and neglected area. The best equipment and maintenance available can be completely offset if personnel do not realize that cracked or frayed insulation, broken strain reliefs, cracked plugs or missing pins, and adhesive tape repairs constitute an electrical hazard. The focus of educational programs must encompass: (a) what constitutes an electrical hazard; (b) what should be done when in doubt about a piece of electrical equipment; and (c) what is the correct procedure for operating this device. The Emergency Care Research Institute is currently evaluating some innovative educational techniques in this area.

Electrical Burns and Electrosurgery

Hard data on the incidence of electrical accidents in the hospital setting are not readily available because of the inhibiting influence of the medicolegal consequences. However, it is safe to say that electrical burns constitute the most common electrical hazard in the operating room. Virtually all electrical burns are associated with the use of electrosurgery or cautery units.

PRINCIPLES OF ELECTROSURGERY. Electrosurgical units are radiofrequency generators. They supply alternating current to the active electrode tip at frequencies between 500,000 and 5 million Hz. The fibrillatory threshold of the myocardium is extremely high at these frequencies and, therefore, electrosurgery does not constitute a fibrillatory hazard (in a properly functioning unit). The current output of these devices is high (up to 1 amp) and because the active electrode tip is small, the current density at the electrode tip is extremely high. It is this high current density that causes local heating and coagulation of the tissue. The current density falls rapidly as it is dissipated through the patient's body (a

conductor of great size) and is returned to the electrosurgical instrument via the return electrode. At the return electrode (patient plate or ground plate, now called dispersive plate), the current density increases again because of the finite area of the plate, but it is not sufficiently high to cause a burn, providing the plate is properly applied.

Extraneous electrosurgical burns are always caused by the existence of return pathways for the electrosurgical current through a body contact with a small surface area. These pathways may include electrodes for electrocardiographic or electroencephalographic monitoring, inadequate area of contact of the patient to the dispersive plate, or inadvertent contact of electrosurgical devices to patients or to operators. The latter is particularly important during laparoscopy or transurethral resection, where the instrument is near the operator's face. Some of the burn hazards of electrosurgical devices have recently been reviewed by C. M. Becker.[1]

A wide variety of electrosurgical units are currently marketed and an increasing number of manufacturers are producing instruments to be used in conjunction with electrosurgical devices (laparoscopes, etc.). In addition, many disposable products for use with electrosurgical devices are being sold. The disposable products constitute primarily electrode assemblies and return plates of various types. Many safety claims are made by manufacturers encompassing the advantages of certain alarm circuits, isolated outputs, solid state electronics, or electrode assemblies. A note of caution is required because none of the safety devices, or claims, is totally effective in eliminating burn hazards.

Significant conduction of radio-frequency energy can occur through apparent insulators or through devices not designed to handle this type of current. For example, some electrocardiographic monitors may offer a low impedance (resistance) pathway for the flow of radio-frequency energy through the patient leads. The practice of clipping electrosurgical cables to the patient using towel clips should be discouraged, since radio-frequency energy can be transmitted through the insulator of the cable and through the towel clip to the patient. Isolated output stages do not guarantee safety or freedom from burns because the patient is commonly grounded by conductive sheeting or by attachment to, or contact with, other electrical devices which, in essence, changes the isolated output stage to a grounded output stage. The relative proximity of other potential electrodes for current flow (EKG, EEG, etc.) to the active electrode can offer preferential, alternate current pathways for radio-frequency energy. Becker has shown that repositioning the indifferent electrode of the electrocardiogram, with respect to the active electrode of the electrosurgical unit, can result in a sixfold or greater reduction in the radiofrequency energy transmitted through it.

The largest dispersive plate is effectively only as large as the actual area of skin contact. Good electrical contact of the return electrode is insured by choosing a site on the patient over a muscle mass, and avoiding bony prominences. The position of the return electrode should be rechecked if the patient moves or is moved during the procedure. Draping should not interfere with patient-plate contact. Some form of electrode

conductive gel should be used with the plate to promote dissipation of electric current and heat. Dispersive plates with sharp corners, folds, or wrinkles can promote localized, high current densities and heating effects since these flaws promote the flow of current to them in much the same way as a lightning rod.

Many alarm circuits can be fooled by the availability of return pathways to the generator other than the dispersive plate. If this return pathway is of sufficiently small area, a burn is a likely possibility. To reduce the incidence of burns, such secondary pathways must be limited. (The use of radio-frequency chokes in EKG electrodes serves this purpose, as does keeping the indifferent electrode of the EKG close to the dispersive plate.) These problems are particularly important during laparoscopy or transurethral resection where the demands for current from the generator are highest. Some authors and manufacturers are recommending multiple grounding points during laparoscopy. Such practices should be discouraged. For example, if the body of a laparoscope is grounded in addition to the dispersive plate, a parallel pathway system is established through which current division will occur. Insulation of the trocar sheath does not completely protect the patient because it does not eliminate extraneous radio-frequency current flow through the body of a laparoscope. If it now is grounded, the potential for current flow through this inappropriate pathway is increased, promoting arcing between the active tip and the body of the instrument. The variety of devices and recommended procedures points to an urgent need for adequate animal studies on the highly technical, but poorly understood, aspects of electrosurgery.

Standards for Electrical Devices

The setting of standards for medical devices and impending medical device legislation will help reduce, but not eliminate, the electrical hazards outlined in this article. The setting of standards is easy when the problems and malfunctions are clearly understood. They become difficult when it is the relationship between several different types of devices which creates the hazard. The difficulties arise not from a lack of standards so much as a lack of data and the mechanisms to generate data. In this sense, it seems more appropriate to define standards for the testing of clinical devices and the analysis of their failures rather than setting standards for the devices themselves. The problems that arise are not unlike the interaction of drugs; however, the mechanisms available for informing users and the manufacturers are much less clearly defined. A great deal of this communication problem could be solved by the manufacturers themselves.

FIRE AND EXPLOSION HAZARDS

A fire is a very rapid combustion or oxidation reaction resulting in the generation of intense heat and light. The probability of a fire or explosion developing within a flammable material and source of oxygen can be enhanced by the following:

Table 1. *Flammability Range of Anesthetic Gases*

DRUG	FLAMMABILITY LIMITS IN AIR (per cent)		FLAMMABILITY LIMITS IN OXYGEN (per cent)	
	Lower	Higher	Lower	Higher
Cyclopropane	2.4	10.4	2.5	60.0
Diethyl ether	1.9	48.0	2.0	82.0
Divinyl ether	1.7	27.0	1.8	85.0
Fluroxene	3.0	—	—	—
Ethyl chloride	3.8	15.4	4.0	67.0
Ethylene	3.1	32.0	3.0	80.0
Halothane	noninflammable		noninflammable	
Methoxyflurane	9.0	28.0	5.2	28.0
Trichloroethylene	noninflammable		10.0	65.0

*Altered from Burns, T. H. S.: Fires and explosions. *In* Wylie, W. D., and Churchill-Davidson, H. C. (eds.): A Practice of Anesthesia. Chicago, Year Book Medical Publishers, Inc., 1966.

1. The occurrence of the reactants (fuel and oxygen) in a gas phase. The gas phase allows complete mixing of the fuel with oxygen, enhancing the probability of molecular collisions and oxidations occurring.
2. The absence of nonreacting components in the mixture such as nitrogen, which serves to dilute the mixture and reduce the probability of collisions between reactants.
3. Increase in the velocity of the molecules within the mixture, which raises the probability of collisions with sufficient energy to cause a reaction. The velocities developed are directly proportional to the temperature of the mixture.

Thus, flammable anesthetic and oxygen mixtures are conducive to a fire or explosion hazard. All that is required is a source of ignition.

Flammable anesthetic mixtures in air have a finite range of flammability and detonability. This range can be expanded by substituting oxygen for air. The lower range can be further extended by the presence of nitrous oxide in the mixture (Table 1). The reason for this is that nitrous oxide itself will support combustion and, in the process of its breakdown, releases the energy of its formation.

Control of fires and explosions in the operating room setting centers around elimination or control of flammable materials and reduction of possible ignition sources. Articles dealing with operating room fires and explosions generally focus on the use of flammable anesthetic drugs. The advisability of eliminating flammable agents from clinical use is the subject of another article in this symposium.* However, it is important to realize that other flammable materials are in common use in the operating room. These include alcohol, other organic volatile prep solutions (acetone, ether), aerosol adhesive sprays, etc. Many of these materials are not labelled as being flammable. In the past decade, the increase in use of disposable products has brought to the operating room large volumes of paper and plastic trash. Although not explosive, these materials are readily flammable and when they burn can liberate smoke

*Ngai, S. H.: "Explosive Agents, Are They Needed?"

and/or toxic fumes. Although complete elimination of flammable materials is not practical, some thought should be given to their control.

Flammable Anesthetics

During the administration of flammable or explosive anesthetic agents, techniques should be geared toward the use of low flow, rebreathing systems. Fire and explosion hazards are always at a maximum during the phase of induction, when the gas flow rates are at a maximum and the necessities for opening the anesthetic circuit are frequent for airway management, laryngoscopy, etc. During emergence, the anesthetic circuit and patient's exhaled gas are once again open to the room; however, concentrations of the anesthetic gas will be lower than during induction. The NFPA code for mixed or explosive anesthetizing locations defines the hazardous zone as a portion of the operating room below the 5-foot level measured from the floor.[2] The basis for defining this zone is that most anesthetic gases are denser than air and, if allowed, will tend to gravitate to the floor level. For this reason the NFPA also recommends that the return air grill be at the floor level.

Although NFPA codes are intellectually satisfying, they have not been backed up by recent data. The modern operating room is a dynamic place; doors are opened and closed, personnel move around, and there is little chance for gas to settle to the floor level in a room of turbulent air currents. Recent studies on trace levels have shown that anesthetic gases are widely dispersed and that "hot spots" (localized zones of concentration) form well above floor level.[5] Unfortunately, the NFPA code does not specify a minimum ventilation requirement for anesthetizing locations which will determine the rate of removal far more importantly than the location of air grills.

Other Flammable Materials

Volatile prep solutions, aerosols, etc. require adequate ventilation, as do the flammable anesthetics. These materials should be handled in such a way that pooling or saturation of patient drapes is avoided. Alcohol-saturated drapes followed by the use of electrocautery represent a significant fire hazard, even in the absence of flammable anesthetics.

Procedures for removing paper and plastic trash from the operating room suite should be frequent and efficient to avoid accumulation in hallways and side rooms.

Elimination or Control of Ignition Sources

Chemical and spontaneous ignition sources are not common in operating room facilities, but local ignition sources are. Common sense dictates that sources of open flame, cigarettes, etc. should be kept well away from operating rooms, recovery rooms, equipment, and storage areas.

Most of the effort to reduce ignition sources is directed to the control of sparks. Conductive floors, anesthetic rubber goods, shoes, upholstery fabrics, casters, etc. are meant to dissipate static charge and prevent the development of large potential differences between objects.

These measures are defeated by waxes, coatings, dirt, and old age. Regular checks of these materials must be made to insure that they remain conductive. Shoe testers should be readily available and used.

Adequate relative humidity promotes the formation of a water film over surfaces and a dissipation of static charges. The relative humidity should be at least 50 per cent. Operating room humidities may vary greatly with the prevailing weather so that spot checks are an inadequate safeguard. Operating rooms used for flammable agents or mixed facilities should have accurate hygrometers to insure that they meet this standard.

Sparks from electrical apparatus can be avoided by the use of equipment specifically labelled "for use in hazardous atmospheres." Electrical equipment not so labelled should be mounted above the mythical 5-foot level in a well-ventilated room. Electrocautery should be banned during administration of agents that are highly flammable or explosive in the clinically used concentration. Extension cords should be banned at all times, since arcing can occur between the electrical contacts. Extension cords are an electrical, fire, and physical hazard in any hospital setting.

SUMMARY

This article has reviewed the physical basis of electrical shock hazards, electrical burns, fires, and explosions in the operating room setting. Control of these hazards is outlined, involving two basic approaches. The first is education; that is, understanding the apparatus, materials, and techniques of safe operation. The second is the maintenance of standards, equipment, and procedures which, when performed in concert, reduce the possibility of equipment failures or accidents.

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Trace Anesthetic Exposure

Consequences and Control

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Chronic exposure to anesthetic gases is a potential health hazard. This was the conclusion of a recent national study of occupational disease in operating room personnel.[1] The interest generated by this report both in the medical community and in the lay press has been amplified by the recent vinyl chloride experience. The purpose of this article is to present the evidence that chronic exposure to trace levels of anesthetic gases is hazardous and to discuss the means available for measurement and control of trace anesthetic levels.

IS THERE A HEALTH HAZARD FROM CHRONIC EXPOSURE TO TRACE CONCENTRATIONS OF ANESTHETIC GASES?

For years anesthetic gases and vapors were felt to be metabolically inert in the body. The deleterious effects on the cardiovascular system and on regional blood flow were reversible once exposure to the agent ceased. Trace levels were felt to be harmless. The earliest evidence suggesting toxicity from chronic exposure was the severe bone marrow depression seen in patients exposed to nitrous oxide for the treatment of tetanus.[13] Subsequent investigators have demonstrated that anesthetics are toxic, at clinical concentrations, to rapidly dividing cells. It should be emphasized that many of these studies were concerned with chronic exposure to clinical levels of anesthetics and not trace concentrations.

In 1968 Bruce et al.[5] reviewed the causes of death among members of the American Society of Anesthesiologists from 1947 to 1966. The causes of death for 441 American Society of Anesthesiologists members were compared with those for U.S. males in general, and with male policyholders of the Metropolitan Life Insurance Company. They found a higher incidence of death from malignancies of the lymphoid and reticuloendothelial tissues in anesthesiologists than in the general popula-

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tion. They concluded that a prospective study was indicated to obtain more reliable data.

A number of investigations have revealed that anesthetic gases are not metabolically inert but, in fact, do undergo biotransformation.[6] Some of the consequences of this biotransformation in patients receiving an anesthetic are detailed below. In the case of some of the halogenated hydrocarbons, fluoride ion formation has been linked to nephrotoxicity.[14] Free radical formation has been demonstrated in the biotransformation of halothane. The formation of free radicals or electrophilic reactants has been hypothesized as a mechanism of carcinogenesis. The possible pathways include: (1) interaction of the carcinogen with DNA, resulting in informational changes in this macromolecule; (2) alterations in RNA protein, resulting in inheritable changes; (3) activation of a latent carcinogenic virus; and (4) selection of preneoplastic cells by conditions favorable to multiplication of these cells. Anesthetics have already been implicated in interfering with DNA-RNA synthesis in investigations of bone marrow depression and teratogenesis.[6]

In studying the effects of chronic exposure to trace concentrations of anesthetics, three primary foci have evolved: (1) the incidence of neoplastic disease among operating room personnel and laboratory animals; (2) the incidence of abortion and congenital abnormalities; (3) the effects of chronic exposure on cognitive skills and the occurrence of perceptual errors.

Incidence of Neoplastic Disease

The evidence that chronic exposure to anesthetics may lead to an increased incidence of malignancy is based on three pieces of evidence. The first was the demonstration by Lassen that chronic exposure to clinical concentrations could depress bone marrow. The second was the report of Bruce of an increased incidence of malignancies of the lymphoid and reticuloendothelial tissues. The third piece of evidence was the reports by Corbett[8] and the Ad Hoc Committee[1] indicating an increased incidence of cancer among anesthetists. However, none of these has been backed up by animal correlates.

Incidence of Abortion and Congenital Abnormalities

Clinical concentrations of virtually every anesthetic have been shown to increase the incidence of abortion in chronically exposed laboratory animals and to increase the incidence of congenital anomalies of their offspring. However, there have been few studies involving chronic maternal exposure to concentrations comparable to the trace levels seen in the operating room. Corbett[9] and Katz[12] have recently shown an increased incidence of fetal and perinatal mortality among rats exposed to concentrations of nitrous oxide and halothane in the parts-per-million (ppm) range. Several studies in the United States, Great Britain, and Scandinavia have pointed to the increased incidence of spontaneous abortion and birth defects in offspring of operating room personnel.[2,7] The evidence that operating room personnel are at greater risk seems convincing at first. Other factors may also be involved. For example, the operating room is a stressful place to work. The control group should

work under similar stress conditions, but not be exposed to anesthetic gases, such as women working in intensive care units. Such studies have not yet been reported. Ideally, the data must show that reduction in chronic exposure levels eliminates or reduces the problem. The Ad Hoc Committee of the American Society of Anesthesiologists is planning such a study in 1978 following a sufficient period of time to allow surgical facilities to institute gas scavenging and monitoring programs to reduce the exposure level.

Effects on Cognitive Skills

Some recent work has demonstrated that performance decrements can be demonstrated following trace anesthetic exposure.[4] The levels involved in these studies were 15 ppm halothane and 500 ppm nitrous oxide in air. The lower limits of a demonstrable effect have not yet been shown. But, obviously, we should be trying to achieve exposure levels well below those used in these studies.

Tolerable Trace Concentration

Exposure levels below 2 ppm halothane and 100 ppm nitrous oxide can be readily obtained in a modern, well-ventilated operating room, even in the absence of scavenging devices. The institution of scavenging and careful technique can reduce these levels significantly. While no official standard has been established, these levels represent a reasonable starting goal in preventing performance decrements until further evidence indicates that lower exposure levels are indicated.

Several forms of exposure to toxic compounds occur. An individual may be exposed to transient levels of relatively high concentrations over short periods of time and/or may be exposed to very low levels for long periods of time. Toxic effects are probably a function of exposure time and dose. The transient periods of highest exposure in the operating room occur upon induction and emergence from anesthesia. At these times the anesthetic circuit is opened to the room and high flows may be used. Exposure to low levels of anesthetics for long periods of time will occur during the maintenance of anesthesia when the circuit is generally closed to the atmosphere and a steady state has been reached. Anesthetic personnel bear the brunt of the exposure since they are continuously in closest proximity to the source of the anesthetic gases. Furthermore, they are generally in the operating room on a daily basis. Supporting personnel (scrub nurses, circulating nurses, etc.) are exposed chronically to low levels; however, these individuals are less likely to be exposed to high transient levels. Surgeons, while they are generally in the operating room only for a segment of the day and frequently operate only 2 or 3 days a week, can be close to the anesthesia source and so be exposed to quite high levels, as well as chronic low levels.

In defining standards, both high transient levels and low chronic levels must be considered. The details of how these exposure levels can be defined and the approaches taken to control them can be compared to those for exposure to vinyl chloride.[10] The vinyl chloride standard defines the permissible exposure limit at 1 ppm averaged over any 8-hour

period, and a ceiling of 5 ppm averaged over any period not exceeding 15 minutes. The standard further defines the concept of a lower concentration, the action level. Where the results of monitoring indicate that no employee is exposed in excess of the action level, then no provisions are required for medical surveillance or monitoring. Where exposures are less than the permissible levels but greater than the action level, monitoring must occur at least quarterly. Where the exposure level exceeds the permissible levels, monitoring must be conducted at least monthly. The employer must take action to reduce exposures to or below the permissible exposure limit.

In the case of anesthetic exposure, the levels reported in the literature indicate that concentrations of halogenated hydrocarbons in the range of 1 to 10 ppm are common. Nitrous oxide exposure levels frequently quoted are in the 50 to 200 ppm range.[17] Other reports have indicated levels may reach much higher concentrations in small, poorly ventilated rooms. It has further been demonstrated that the use of anesthetic gas scavengers* can significantly reduce the exposure level.[16] The utilization of scavenging systems, effective ventilation in the operating room, low gas inflows, elimination of leaks, and care in technique to avoid spillage of gases during induction results in levels well below 100 ppm N_2O and 2 ppm of halogenated hydrocarbon. Hard data regarding the exposure levels which are absolutely safe do not yet exist.

MONITORING METHODS

Although nitrous oxide has no odor, one can often smell the presence of a halogenated hydrocarbon anesthetic. Preliminary studies in our laboratory indicate the most frequent minimum concentration necessary for someone to detect the odor of halothane is 50 ppm, well in excess of the performance decrement limit. Obviously, perception of the odor of a halogenated anesthetic is evidence for excessive levels. More objective monitoring involves taking routine air samples in the area of the anesthetic machine during an actual case. The gas samples obtained can be assayed by gas chromatography, mass spectrometry, or infrared analysis. Gas sampling containers and analysis services for operating rooms are currently commercially available. The sampling containers must be leakproof and remain so through the rigors of handling, transport, and large changes in ambient pressure as might be encountered during transport in an aircraft. The contaminant levels involved are extremely small; hence, all components of sampling containers must be inert so that absorption or adsorption of the anesthetic traces does not occur. Containers with plastic components are apt to introduce significant errors into the monitoring process. Precise standards of the gases to be measured must also be available.

An initial monitoring program should involve spot sampling of more than one location throughout the operating room. Obviously, the area of

*A variety of scavenging devices are available. Their purpose is to capture "pop off" gases and conduct them to the ventilation or suction systems, thereby eliminating spillage into the operating room.

the anesthesia machine is that of highest exposure. However, recent studies have shown that airflow patterns in the operating room may promote the formation of significant stagnant areas where the clearance of these gases may be slow.[16] These have been termed "hot spots." Studies in our own operating rooms have indicated that the location of the ventilating ducts and exit ducts relative to the anesthesia machine is extremely important in the clearance of these materials. Anesthetic gases do not settle to the floor level as described in most anesthetic textbooks, but are rapidly dispersed in the turbulent air currents that are common in the modern operating room. The airflow patterns vary widely from room to room. As a consequence, we have developed the concept of "effective room ventilation." This is determined by measuring the steady state level of N_2O achieved in a room at the site of the anesthesia machine from which a standard load of nitrous oxide (3 L per min) is delivered. We have arbitrarily defined an adequately ventilated room as one in which the steady state level of nitrous oxide achieved is less than 100 ppm with this 3 liter per minute load in the absence of scavenging.[15] This represents an "effective ventilation" of 30,000 L per min.

Another approach involves determining time-weighted average exposure, which is the product of trace level and exposure time, using an integrating sampler. Personal integral samplers are currently used in industrial pollution control. These samplers are directly analogous to the radiation badges worn by x-ray personnel. Integral gas samplers for operating room personnel are currently under development.

HOW CAN EXPOSURE LEVELS BE REDUCED?

Ventilation and scavenging are the primary control mechanisms. Ventilation is usually defined in terms of the number of air changes in the room on an hourly basis. Although a minimum standard for the operating room in air changes per hour has not been defined by any regulating body, most modern rooms are provided with at least 10 air changes per hour. Many bacteriologists suggest that perhaps 20 air changes per hour are necessary for the control of microorganisms. The NFPA defines the relative height locations of the supply grill and the return air grill within the operating room, but it does not define grill locations relative to the anesthesia machines. Nor does it recommend a minimum ventilation flow rate. Ideally, the anesthesia machine should be located as close as possible to the exhaust grill of the operating room ventilation system. Obstructions to the flow of air within the room creating stagnant areas or "hot spots" should be avoided.

In recent years, in an attempt to conserve energy, many new operating rooms have been designed with ventilation systems incorporating the recirculation of operating room air. Although recirculation represents a potential hazard in the problem of chronic exposure to anesthetics, the important factors are the total fresh airflow into the system and the proportion of recirculated air. In our own operating rooms we have found no significant difference in the mean levels of anesthetic gases

between rooms in which there is recirculation, as compared to rooms ventilated with 100 per cent fresh air. However, cross contamination of rooms on a common manifold does occur. It is apparent that some minimum standards must be defined regarding volume flow rates required for an operating room, the permissible proportions of recirculation, and the ideal arrangement of the geometry of the ventilator grills.

The second major control mechanism for operating room pollution is the use of an anesthetic scavenging device. A number of these devices are currently available. Such a device should not leak when challenged with large boluses of popped-off gas from the breathing circuit. Many of the available devices do not meet this standard. Excess gas must also be exhausted or trapped in such a way that it does not get mixed with the bulk of the operating room air. Many devices perform this function by venting through the room's suction line. However, adequate reservoirs for the exhaust gas must be present and adequate suction flow must be provided. Positive pressure applied to the airway of the patient will cause excess gas flows through the pop-off valve into the scavenger at rates of between 10 and 50 L per min. This peak flow rate must be handled by suction line flow rate and/or a reservoir, or else exhaust gas will be dumped directly into the room. Other scavenging devices use activated charcoal as a mechanism for adsorption of the exhaust gases. Activated charcoal is an effective trap for halogenated hydrocarbons but does not adsorb nitrous oxide. Unfortunately, the bulk of the evidence suggests that nitrous oxide is the agent which represents the most significant health hazard. One effective scavenging system directs the excess gas directly to the exhaust grill of the operating room ventilation system.[3] This method, however, is cumbersome and awkward. There is considerable room for innovation in this field.

Other considerations in the control of exposure levels involve using anesthetic techniques with low gas flows or closed systems or the avoidance of inhalation agents. Unfortunately, use of regional anesthesia is not satisfactory for all types of surgery, and patient acceptance is limited. The exploration of hypnotic and acupuncture techniques currently in vogue may be helpful. The development of suitable short-acting intravenous drugs would be advantageous if they did not require supplementation with nitrous oxide.

SUMMARY

Epidemiologic and animal studies indicate that chronic exposure to anesthetic gases may constitute a potential health hazard. This is suggested by a higher incidence of spontaneous abortion among female operating room personnel, congenital anomalies in the offspring of operating room personnel, and neoplasia of the reticuloendothelial system. Human data show that performance can be compromised during exposure to anesthetic traces. A direct cause and effect relationship between anesthetic exposure and the alleged hazards will require further prospective studies. Such a study is being planned by the Ad Hoc Committee of the American Society of Anesthesiologists. In the interim,

monitoring programs should be established to define adequate clearances of the anesthetic agents. Minimum standards and recommended procedures should be established regarding operating room ventilation and design. The use of effective scavengers and anesthetic techniques not requiring the use of inhalational agents should be encouraged. In this way a clear distinction may be defined by the prospective study planned by the American Society of Anesthesiologists in 1978.

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Explosive Agents—Are They Needed?

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In order to answer the question of whether explosive anesthetics are needed, a number of associated problems have to be discussed. These include: (1) advantages of these anesthetics aside from explosive hazards; (2) advantages and disadvantages of presently available nonexplosive anesthetics; (3) the current trend in the practice of anesthesiology concerning the use of explosive anesthetics and reasons for this trend; (4) the revised code of The National Fire Protection Association (Bulletin 56A, 1973) concerning construction, services and conduct of personnel in hazardous locations.[24]

It is not the purpose of this article to state categorically that explosive anesthetics should or should not be used. Professional judgment, individual bias, long-standing habits, cost, and convenience factors all have bearing on this question. Public debate on continued use of explosive anesthetics in recent years has been mingled with emotional exchanges. Straw votes taken during these occasions were usually in favor of continued use of explosive anesthetics. One suspects that an individual's own professional judgment and freedom to prescribe in his or her clinical practice are at stake. Most, if not all, specialists in the discipline are not yet ready to forego their prerogatives in the choice of drugs.

When surgeons or internists follow a certain course of action in treating their patients, they exercise their professional judgment or individual bias within the constraints of accepted practice and standards. Anesthesiologists have the same obligation to their patients in that for a given patient undergoing a given procedure requiring anesthesia, a "routine" anesthetic procedure, such as "a touch of Pentothal" or "a whiff of gas," is not acceptable (no more acceptable than a standard Billroth's I or II operation for every patient with gastric ulcer). Fortunately the choice of anesthetics and techniques of administering them is wide so that a competent clinician can indeed make a sound decision even with certain limitations in agents and facilities. However, if he or she should decide to administer an explosive agent, the decision would

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necessitate many precautions involving construction of anesthetic locations, electrical circuitry, and design of equipment, as well as choice of footwear and clothing of personnel. Therefore, the question is not just a matter of individual prerogative. It should be considered in terms of objective merits of explosive anesthetics, costs involved in conforming with the safety code to prevent fire and explosion, and indoctrination of all personnel in and around anesthetic locations.

ADVANTAGES AND DISADVANTAGES OF EXPLOSIVE AGENTS

Explosive anesthetics include cyclopropane, diethyl ether, and ethylene. These agents, except the latter, have been used with some degree of frequency in the recent past, and are still being used although there are no reliable overall statistics in this country or abroad. Fluroxene (Fluoromar) is another anesthetic having potential fire and explosion hazard. In air or oxygen, fluroxene has a lower limit of flammability of 4 per cent (v/v),[17] often exceeded during induction of anesthesia.

What are the advantages of these agents? Pharmacologic actions of anesthetics have been discussed in detail elsewhere in this issue. Only salient features of each of the explosive agents will be briefly mentioned here.

Cyclopropane

Cyclopropane is a fast-acting anesthetic bacause of its relatively low solubility in blood (blood/gas partition coeffecient, 0.42).[9] Induction and recovery are rapid, and depth of anesthesia is readily adjustable to suit the requirement of surgical procedures. This is due to the fact that equilibration between the inspired concentration and that in alveolar air, arterial blood and brain, occurs faster than it does in the case of other anesthetics, with the exception of nitrous oxide and ethylene;[26] and both of these require supplementation to provide adequate anesthesia. Cyclopropane is a fully potent agent so that it can be administered alone with oxygen. Adjuvant drugs, such as muscle relaxants, if needed, may be given in smaller doses. Those who believe in a simplistic approach in anesthetic practice may consider this feature of cyclopropane desirable as few drugs are required.

A unique characteristic of cyclopropaine is its action on circulation. Except during extremely deep anesthesia using high concentrations (>40 per cent), which is rarely necessary, cardiac output and arterial pressure are well maintained or perhaps even increased.[15] Proponents of cyclopropane anesthesia believe that in patients suffering from massive hemorrhage, hypovolemia, and shock, the use of cyclopropane is beneficial. Perfusion of brain and heart might be kept at the best possible level. However, this may or may not be truly advantageous as arterial pressure is maintained at the expense of intense peripheral vasoconstriction, including that of the liver and the kidney.[7, 25] This is not consistent with current concepts in the management of shock. At best, cyclopropane anesthesia under this circumstance should be regarded as

a temporizing measure, allowing surgeons to control continuing hemorrhage while attempts are being made to correct volume deficits.

Cyclopropane has a propensity to sensitize the heart toward catecholamines, exogenous or endogenous, resulting in apparently disturbing arrhythmias.[23] Exogenous sources of catecholamines can be avoided easily, whereas endogenous release of catecholamines may occur in response to surgical stimuli during light anesthesia. Ventricular arrhythmias also occur during deep cyclopropane anesthesia and/or hypercarbia.[22] It should be noted, however, that arrhythmias during anesthesia are usually transient, readily amenable to simple measures such as cessation of surgical manipulation, improved ventilation, and adjustment of anesthetic concentration. Treatment with antiarrhythmic drugs is seldom necessary. Since the early 1950s when it was realized that hypoventilation and its complications occur frequently during anesthesia, practice has been changed so that hypercarbia is now rarely a cause of concern. Rather, possible detrimental effects of hyperventilation and consequent hypocarbia have concerned researchers and clinicians alike in recent years.[1]

It would seem that except for explosive hazards cyclopropane is an excellent anesthetic. But, to exploit its pharmacologic properties one must first master the practical aspects in its administration. Since the use of cyclopropane has decreased drastically during the past decade, students in anesthesiology are no longer being fully trained in its use.

Diethyl Ether

Diethyl ether was the mainstay of anesthetic practice for about a century before modern anesthetics and muscle relaxants became available. One recalls with nostalgia the use of minimal and primitive equipment in learning and teaching the technical finesse necessary to effect smooth induction. Due to its high blood/gas partition coefficient (12),[9] diethyl ether requires longer duration for induction and emergence. Yet, virtuosos of the old school take pride in their ability to induce ether anesthesia smoothly and have their patients regain vital reflexes in the operating room! Recovery rooms were not always available.

Sentiments aside, are there advantages to using ether? It has been stated that ether is a safe agent because of its high solubility in blood. Changes in depth of anesthesia occur rather slowly. But this relative safety factor can be obviated by efficient out-of-circuit vaporizers. High concentrations of ether can be and have been introduced into anesthetic breathing systems. Protective reflexes such as breath holding and coughing may be abolished by muscle relaxants. Inadvertent overdose did occur back in the 1950s when out-of-circuit precision vaporizers were first introduced. Of course these mishaps could occur with all potent anesthetic vapors and should not be attributed to ether exclusively.

There are a number of disadvantages with ether. Slow induction and emergence have been mentioned. Unless ether is well administered, stormy anesthesia, copious secretion, and postanesthetic nausea and vomiting are most unpleasant, adding to anesthetic hazards. Here again one must ask the question if skill in administering ether is being taught in our resident training programs.

Ethylene

Ethylene is an anesthetic gas having a potency slightly greater than that of nitrous oxide, but not enough to produce the state of anesthesia when administered alone. It is a matter of opinion whether the difference in potency between ethylene and nitrous oxide is significant. Supplemental drugs such as barbiturates or narcotics are needed with either anesthetic. One may have the impression (without supporting data) that doses of supplemental drugs required are smaller when using ethylene. Ethylene is said to have minimal depressing effects on circulation and respiration. But flammability and the pungent odor of ethylene (to patients and surgical team) are distinct disadvantages offsetting its questionable advantages. In addition, it is the only anesthetic agent lighter than air. This factor makes the placement of electrical connections above the 5 foot level a hazard, rather than the safety precaution which it is with other agents.

Fluroxene

Fluroxene (Fluomar) is an effective agent with characteristics of cyclopropane in that it supports the circulation, and of ether in that it often causes increased minute ventilation. However, it does not provide quite as profound muscle relaxation as do these other agents. It is explosive at concentrations of greater than 4 per cent in nitrous oxide and oxygen, but satisfactory maintenance of anesthesia can be achieved below that range in a majority of cases. Many anesthetists use it in conjunction with electrocoagulation. Though several explosions have been reported during clinical use, no one has been harmed.

NONEXPLOSIVE ALTERNATIVES

We have a good number of nonexplosive anesthetics. Inhalational agents include halothane (Fluothane), methoxyflurane (Penthrane), enflurane (Ethrane), and nitrous oxide. All except nitrous oxide are fully potent, halogenated anesthetic vapors. In the process of being tested clinically is another halogenated ether, isoflurane (Forane), which seems to have promise as an excellent anesthetic. In addition to thiobarbiturates, thiopental (Pentothal) and thiamylal (Surital), a number of other intravenous agents have been used frequently to induce anesthesia and to supplement nitrous oxide. Narcotics such as meperidine (Demerol), fentanyl (Sublimaze), and morphine, are quite popular. Recently morphine is being administered in large doses (1 to 2 mg per kg or more) alone or together with nitrous oxide in poor risk patients for major operations (such as open heart procedures).[21] Other compounds such as droperidol (Inapsine), diazepam (Valium), and ketamine (Ketalar), have been used with varying frequency, depending on individual anesthesiologists' personal preference or bias.

Halothane

Since its introduction in 1956, halothane has been administered to millions of surgical patients. Anesthesiologists are attracted to this

agent because of its potency, moderate solubility (blood/air partition coefficient, 2.2)[9] which allows relatively fast induction, ready control of depth of anesthesia, and prompt recovery. With modern precision vaporizers halothane may be considered "easy" to administer. (The word "easy" must be qualified as halothane, like all potent anesthetics, is lethal if administered without knowledge of its pharmacologic action and without proper use of anesthetic equipment.) "Deep" halothane anesthesia is always associated with significant cardiovascular depression.[28] This problem is readily managed by administering minimal anesthetic concentrations adequate to produce sleep, by using halothane in conjunction with nitrous oxide and thus reducing the halothane concentration required,[27] and by the use of muscle relaxants when necessary.

Halothane causes cerebral vasodilation, resulting in increase in intracranial pressure, an action considered not desirabie in patients having space-occupying lesions of the brain.[14] This action is shared by other potent anesthetic vapors as well. It should be mentioned that, prior to accurate monitoring of intracranial pressure during anesthesia, thousands upon thousands of craniotomies were performed under halothane anesthesia. As cerebral blood vessels retain their responsiveness to carbon dioxide tension in the presence of halothane,[29] perhaps the common practice of hyperventilation with resultant cerebrovasoconstriction can attenuate the cerebral vasodilating effects of halothane and other potent anesthetics in neurosurgical patients.

For more than 10 years the medical profession has been engaged in the discussion, often emotional, of hepatotoxicity of halothane *and* other halogenated agents. An extensive national retrospective survey yielded no definitive answer to the question—is halothane responsible for the rare occurrence of massive hepatic necrosis after its use?[3] There is agreement that halothane is not a direct hepatotoxin in the classic sense, as is the case with carbon tetrachloride and chloroform. Beyond this we have made little progress. The possibility of hypersensitivity to halothane or its metabolites has been proposed on the basis of two reports.[2, 16] It seems that the major obstacle in settling this issue is a lack of definitive diagnostic tests for either "halothane hepatitis," as it is commonly called, or viral hepatitis. Diagnosis is by inference after ruling out other possible causes. A recent symposium summarized current views on both sides of the Atlantic.[8]

In summary, halothane is an excellent anesthetic but not an ideal one. There are no reliable statistics to support the view that anesthetic complications following halothane anesthesia are less frequent. Rather, skills of anesthesiologists may be the more important factor in preventing complications. Nevertheless, whatever is most convenient for anesthesiologists should improve the lot of their patients.

Methoxyflurane

Methoxyflurane shares many of the attributes of halothane except that it is more soluble in blood (blood/air partition coefficient, 12) and in fat.[9] Recovery after prolonged anesthesia can be delayed as adipose tissue serves as a reservoir, slowly releasing the drug following the termination of its administration. It is an excellent skeletal muscle relaxant.

But the availability of neuromuscular blocking compounds obviates the need to produce muscle relaxation with anesthetics themselves.

Methoxyflurane is extensively metabolized. As much as 50 per cent of methoxyflurane remaining in the body at the end of anesthesia is degraded, yielding a number of metabolites, including organic and inorganic fluorides.[13] Inorganic fluoride concentrations in blood may increase to as much as 50 μM per l.[5] This is believed to be responsible for renal dysfunction following methoxyflurane anesthesia. Tubular reabsorption of water is inhibited resulting in polyuria and dehydration, not responding to antidiuretic hormone.[6] This complication is related to the dose of methoxyflurane, and is seldom fatal if detected and properly treated. The use of methoxyflurane has been significantly curtailed during the past few years.

Enflurane

Enflurane is a heavily halogenated ethyl methyl ether which became available for clinical use in 1973. Reflecting the current trend in the development and introduction of new anesthetics, enflurane has been thoroughly studied in respect to its chemical and physical properties, potency, uptake and disposition. In addition there have been numerous clinical trials. There are many points of similarity between enflurane and halothane in their actions. But differences exist. Enflurane, being an ether, results in a more stable cardiac rhythm. Its action to relax skeletal muscles is more prominent than that of other anesthetic hydrocarbons.[18] In contrast to methoxyflurane, enflurane is metabolized to a much smaller extent, less than 3 per cent.[4] Thus, excessive serum inorganic fluoride levels are not expected. Nevertheless, there has been one report on the possible renal toxicity of enflurane in a patient with pre-existing renal disease.[20] Another feature of enflurane not shared by other halogenated anesthetics is the occasional appearance of seizures, most of the time manifested in electroencephalogram only. Seizures, electric or somatic, are more likely to occur during deep enflurane anesthesia, especially when there is hypocarbia from hyperventilation.[19] However, clinically this side effect of enflurane has not been a serious problem.

Isoflurane

Isoflurane, an isomer of enflurane, is still undergoing clinical trials at present. It is minimally metabolized. In man, organic fluoride is the predominant end-product.[12] Isoflurane does not have as great a propensity as enflurane to produce seizures.[10]

Supplementary Drugs

All intravenous anesthetics including narcotics are being used to supplement nitrous oxide. Anesthetics administered parenterally share one common disadvantage, that is, once the drug is given it must be degraded by the body. Initial redistribution of the drug to tissues accounts for the apparently short duration of action of some intravenous anesthetics such as thiobarbiturates. When rather large doses of these drugs have been administered it is expected that full recovery will be

slow. Under certain circumstances clinicians may take advantage of the long duration of drug action in that patients may have satisfactory analgesia, and may tolerate an endotracheal airway and mechanical ventilation in the immediate postoperative period. Good recovery room facilities and nursing personnel are essential for this practice.

Skillful anesthesiologists usually try to use the smallest dose of barbiturates or narcotics possible, compatible with adequate depth of anesthesia and pain relief. One must always be on the alert to avoid inadvertent "wakefulness" during surgery while the patient is being paralyzed with muscle relaxants. On the other hand, excessive doses of intravenous agents lead to hazards of prolonged recovery and respiratory and cardiovascular depression. For barbiturate overdose, analeptics are not satisfactory as reliable or desirable antidotes. Naloxone (Narcan) is quite effective in reversing the depressant actions of narcotics, but the duration of action of naloxone is short, 30 to 45 minutes.[11] Therefore, continued surveillance is essential and repeated administration of naloxone may be necessary. In the case of droperidol and ketamine, judicious use is the only way to avoid delayed recovery.

The problems occurring with use of intravenous anesthetics do not suggest that these agents are poor or second choices. But those who choose this mode of anesthesia must be thoroughly knowledgeable in the areas of pharmacokinetics and drug interactions. They must anticipate the need to maintain unconsciousness (at least amnesia) and analgesia during surgery, so that the dose administered is appropriate to avoid mishaps. It is very easy to inject drugs intravenously but the consequences of misjudgment could be serious and sometimes fatal.

Regional anesthesia is suitable for many surgical procedures. The choice of local anesthetics is wide. Recent introduction of long-acting agents such as bupivacaine (Marcaine) and etidocaine (Duranest) has extended the utility of regional anesthesia for operations expected to last longer than 2 to 3 hours. The problem with regional anesthesia is a matter of public acceptance. Many patients do not wish to remain "awake," or are ill-informed about rare complications. If reliable statistics were available comparing incidences of complications of general anesthesia versus regional anesthesia one would not be surprised if regional anesthesia proved to be safer. Perhaps surgeons and anesthesiologists should attempt to persuade their patients to accept regional anesthesia when circumstances permit. Surgeons may have to adapt somewhat to operate on patients under regional anesthesia, to manipulate tissues more gently, and to move faster. There are a number of institutions in this country where regional anesthesia is being used with great frequency. In countries where medical equipment and supplies are not so abundant, regional anesthesia is practiced out of necessity.

In summary, the variety of agents now available would make it seem that we can do very well without explosive anesthetics.

CURRENT TRENDS IN USE OF EXPLOSIVE AGENTS

Let us now examine the trend in the use of explosive anesthetics. According to sales figures of one major manufacturer of medicinal

gases, in 1966, 4.3 million gallons of cyclopropane were sold; in 1973 sales were 1.4 million gallons, much of which was exported. Three other companies have stopped manufacturing cyclopropane.* At the Hospital of the University of Pennsylvania during the years 1960–62, approximately 40 per cent of anesthetic procedures were conducted using explosive anesthetics; in 1972–73, 5.7 per cent (Prevoznik, S. J.: Personal communication). At the Columbia-Presbyterian Medical Center, downward trends in the use of cyclopropane, diethyl ether, and ethylene are striking: in 1964, cyclopropane was used in 18.9 per cent of procedures; diethyl ether, 4.6 per cent; and ethylene, 3.1 per cent. In 1969, the frequency of use of these three agents dropped to 8.7, 1.8, and 1.0 per cent respectively. And, in 1973, the total use of all three anesthetics amounted to barely 1 per cent. It seems certain that in this country and throughout the world, explosive anesthetics are now being used infrequently.

Two major reasons may be cited for this remarkable change in anesthetic practice. One is the development of potent nonexplosive anesthetics, the halogenated hydrocarbons and ethers. These new anesthetics have a history of less than 20 years but have found wide acceptance among anesthesiologists. Additionally, the increasing use and familiarity with intravenous anesthetics, such as narcotics, butyrophenone derivatives and other compounds, allows wider choice of anesthetics to suit a given patient for various surgical procedures.

The widespread use of electrical devices in the operating room is the other factor. More and more surgeons are relying upon electrocautery for hemostasis, out of necessity or for expediency. It would not be feasible or popular to ask surgeons with established operative techniques and habits to abandon electrocautery for the sake of using explosive anesthetics if alternatives are available. If nothing else, one must consider the extra operating time involved.

Careful monitoring of patients' vital signs during major surgery is becoming a matter of routine for optimal care. This practice may be considered an advance, enabling anesthesiologists and surgeons to follow closely their patients' status, especially during operations on the heart and major vessels, and major neurosurgical and orthopedic procedures. Monitoring of circulatory status on a continuous basis is greatly facilitated by electronic equipment. Safety precautions are concerned not only with explosions but with electric shocks and burns from current leak and improper power supply to the operating suite.

THE REVISED SAFETY CODE

Bulletin 56A of The National Fire Protection Association, published in 1973,[24] imposes strict standards for "flammable anesthetizing locations" (or "hazardous locations"). New surgical facilities, for economic reasons, are being constructed according to standards set forth for "non-

*Dr. Robert T. Donham obtained this information from manufacturers of medicinal gases in the United States.

flammable anesthetizing locations." Certain hospitals have changed or are proceeding to change "hazardous locations" to "nonflammable anesthetic locations." Other hospitals, seeking to retain the capability for continued use of explosive anesthetics, have resorted to "mixed facilities," that is, one or more operating rooms are designated as "flammable anesthetizing locations." It is only in these rooms that explosive anesthetics may be used.

On the surface the arrangement of "mixed facilities" seems reasonable, so that if in the opinion of anesthesiologists an explosive anesthetic is indicated, anesthesia and operation can be performed in "hazardous locations" according to the safety code. However, in practical terms, it is not so simple to manage busy operating room schedules in this way in a large hospital. Scheduling of operation is already difficult, requiring much arrangement and rearrangement to accommodate unforeseen circumstances and other obligations of surgeons and anesthesiologists. In most cases, anesthesiologists do not visit their patients until operating room schedules have been finalized. A decision to use an explosive agent at that time could create havoc in scheduling.

Additionally, the safety code (NFPA Bullentin 56A) seems to have nullified possible advantages of "mixed facilities." Bulletin 56A states, "all equipment intended for use in both flammable and nonflammable anesthetizing locations shall meet the antistatic requirement of Section 46" (section 6141). This means equipment to be used in nonflammable locations shall be either fixed or explosion proof. Further, according to sections 6143, 6144, 6145, and 6146, portable x-ray and electric equipment to be used in "mixed facilities" shall "comply with the requirements" for that approved for hazardous locations. Section 6142 appears to allow that "equipment intended for use only in nonflammable anesthetizing locations shall be labeled . . . and shall not be introduced into flammable anesthetizing locations." This is more easily said than done. One must be on the lookout constantly for human errors.

In one medical center one operating room has been designated as the "flammable anesthetizing location" but it is seldom used. Is it economical or reasonable to maintain surgical facilities not being utilized? Ideally, if an explosive anesthetic is indeed the best choice, one should have the opportunity of using it. But there are few situations when the anesthetic choice is so clear-cut.

EVALUATION

The question is not whether explosive anesthetics are needed. Alternative drugs are available. Rather the question is whether physicians' personal preferences and prerogatives can outweigh the cost and other inconveniences involved in the continued use of explosive anesthetics. In spite of the fact that some training centers wish to continue the use of these drugs, and some physicians believe there are cases where these agents are specifically indicated, the use of explosive agents is rapidly decreasing to a very small percentage of cases. Reasons for this include

more that just the cost of maintaining "hazardous locations." The inconvenience of training and policing the surgical team in explosive precautions is important. So, too, is the increasing likelihood of human error as experience with these agents becomes vanishingly small. Perhaps the least medically justified reason for decrease in use of explosive agents is the one which weighs so heavily in the minds of many—medicolegal risk. Considered in perspective, the incidence of explosions is very small compared to the incidence of anesthetic morbidity and mortality from other reasons.

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Postanesthetic Complications

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Instability characterizes the immediate postoperative course when the patient emerges from drug-induced coma (general anesthesia) or sensory, motor, and sympathetic blockade (regional anesthesia). Many physiologic disorders, easily recognized in the fully responsive and unanesthetized patient, are modified, ablated, or eliminated entirely by residual anesthesia, presenting a major difficulty in the postanesthetic patient. Furthermore, the patient's response to therapeutic efforts to correct such disorders will also be altered by the residual anesthesia.

In this chapter, we will discuss four categories of postanesthetic problems: respiratory, cardiovascular, and metabolic complications, and postoperative pain and delirium. Awareness of these complications will hopefully improve their recognition and reduce or, better still, prevent morbidity.

RESPIRATORY COMPLICATIONS

Airway Obstruction

Airway obstruction most often results from soft tissues infringing on the upper airway. The tongue can and frequently does occlude the pharynx if the patient lies supine with his head flexed.[41] A large tongue or anterior epiglottis and larynx predispose the patient to airway obstruction. Obstruction of the pharynx or larynx can occur following head and neck surgery when the head cannot be positioned optimally, or if such surgery causes edema.

Physical examination of a patient with such an obstructed airway may reveal flaring of the nares, retraction at the suprasternal notch (tracheal tug) and intercostal spaces, little or no elevation of the anterior chest wall, and vigorous diaphragmatic and abdominal contractions. Auscultation discloses inspiratory stridor, high or low pitched breath sounds, or worse yet, no breath at all!

When the patient is supine, hyperextension of the head (if possible) may relieve airway obstruction. The mandible is lifted cephalad and upward by curling both index fingers around the rami of the mandible (jamming the index finger into the mandibular ramus causes point tenderness). Both thumbs should oppose each other on the mandibular symphysis, pushing the chin caudad and posteriorly to open the mouth.

When the patient is on his side, the upper airway is less likely to obstruct because the tongue falls forward naturally. However, soft tissue obstruction occurring in this or the prone position may go unnoticed and lead to hypoxia.

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Laryngospasm during emergence from general anesthesia is another common complication. Suctioning, airway manipulation, and oral or nasopharyngeal airways may cause it. One should deliver 100 per cent oxygen by bag and mask with positive pressure. Most patients will respond to this maneuver. Occasionally, however, laryngospasm can continue to the point of hypoxia. Then, a small dose of succinylcholine (10 to 20 mg intravenously) may be necessary to break the spasm and allow assisted ventilation with high oxygen concentrations to proceed.

Many factors contribute to laryngeal trauma and edema.[30, 33, 54] Corrective therapy includes sitting the patient erect, maximally humidifying inspired gases, administering nebulized racemic epinephrine accompanied by either spontaneous or positive pressure ventilation, administering dexamethasone – 10 mg intravenously – or inducing a diuresis with furosemide 10 to 20 mg intravenously. Laryngoscopy may detect remedial lesions.[33] In children, laryngeal edema can rapidly progress to complete airway obstruction. Both personnel and equipment for emergency laryngoscopy, bronchoscopy, and tracheostomy must be close by.

Bronchospasm

Bronchospasm occurring early postoperatively is rarely due to asthma but more likely to airway obstruction from a misplaced or malfunctioning endotracheal tube or to irritation of the airway during anesthetic emergence.[29] It is also an early sign of acute pulmonary edema, preceding rales and frothy sputum. Occasionally a patient with a history of smoking and chronic bronchitis will suffer bronchospasm postoperatively. In any event, excessive work in overcoming airway resistance makes ventilation difficult for the partially anesthetized surgical patient. Merely removing the endotracheal tube will often alleviate bronchospasm. Aminophylline for relief of bronchospasm in the immediate postoperative period carries with it some risk. In the partially anesthetized, potentially or actually hypoxic and hypercarbic patient, the margin of safety between relief of bronchospasm and development of arrhythmias is narrow.[10] If the patient requires positive pressure ventilation, isoetharine (Bronkosol) can be nebulized and administered as an aerosol. If the patient can breathe spontaneously, a nebulizer mask will allow him to handle the bronchodilator aerosol. If the severity of bronchospasm precludes delivery of aerosol particles to specific constricted airways, intravenous infusion of isoproterenol or epinephrine almost always successfully reduces bronchospasm.

Hypercarbia

Postoperative hypercarbia results from inadequate respiratory drive, inadequate function of respiratory muscles in response to an appropriate respiratory drive, intrinsic lung disease, or increased CO_2 production.

Inadequate central respiratory drive may result from a pre-existing disease state, residual anesthesia, an inhalation agent or narcotic, or occasionally, a neurosurgical procedure.

Among the many factors contributing to *inadequate ventilatory mechanics* are the patient's position,[34] obesity, ascites, the site of incision, the degree of postoperative analgesia, residual neuromuscular blockade, the type of dressing binding the wound, and acute gastric dilatation. The surgical procedure itself may make the maintenance of normal respiratory mechanics difficult or impossible when, for example, residual pneumo- or hemothorax or pleural effusion develops. Chest wall and lung compliance decrease following thoracic and upper abdominal surgical procedures. Therefore, just when greater effort is required to produce a given tidal volume, that effort is diminished by body position or pain. Preoperative evaluation can help determine the extent to which recovery is expected. A patient with chronic bronchitis and emphysema has an airway which responds irritably to endotracheal intubation or airway manipulation. The increased airway resistance concomitantly increases work of breathing. In the patient unable to respond to this stress, P_aCO_2 rises.

Increased CO_2 production due to emergence excitement, shivering, or hyperthermia may also lead to hypercarbia if the patient cannot or will not increase alveolar ventilation.

Signs and symptoms of hypercarbia not only vary with the previously mentioned causes but are modified by the type of anesthetic used. When respiratory drive is depressed, respiratory rate may be slow and tidal volume shallow. Yet residual narcotic may cause increased tidal volume without visible airway obstruction or chest wall retraction at a depressed rate. Hypertension and tachycardia may also be absent due to circulatory depression. When respiratory drive is normal but ventilatory response inadequate, the respiratory rate may be rapid but tidal volume shallow. In addition, the anterior chest wall may retract, the diaphragm and abdominal muscles accounting for what little tidal volume exists.

Assuming that CO_2 production and gas distribution were normal, one could infer hypercarbia by measuring reduced minute ventilation. Similarly, normal minute ventilation ought to produce normocarbia. Unfortunately, postoperatively, CO_2 production and wasted ventilation can occur unpredictably, rendering inferences of alveolar ventilation from minute ventilation inaccurate. In addition, hypercarbia occurs in the presence of normal minute ventilation if wasted ventilation is elevated. Hence direct measurement of P_aCO_2 is necessary for definitive diagnosis of hypercarbia.

Measurement of vital capacity integrates (1) the mental ability of the patient to initiate a deep breath in response to command, (2) respiratory drive, (3) chest wall and lung mechanics, and (4) intrinsic pulmonary disease. A vital capacity as low as 10ml per kg or approximately two times the predicted tidal volume is barely acceptable.[48] When this criterion is absent, the likelihood of atelectasis, hypoxia, and hypoventilation increases. Inspiratory force also tests respiratory function even in the absence of consciousness.[59] While the inspiratory force generated by a normal subject is greater than −100 torr, it is usually reduced to −30 to −40 torr in the postoperative patient.

If respiratory depression is drug-induced from residual anesthesia but the patient remains capable of generating an inspiratory force greater than -20 torr, then in most cases spontaneous emergence from anesthesia combined with a stir-up regime will restore normal respiration. Controlled ventilation may be used to maintain normocarbia; the resultant increased alveolar ventilation will accelerate removal of the inhalation anesthetic and shorten emergence.[54] If the residual anesthetic effect is due to narcotic, the injection of an intravenous narcotic antagonist – naloxone 0.2 to 0.4 mg intravenously – will result in immediate arousal and awakening.[24] It is imperative that the patient be closely observed since the narcotic's duration of action may be considerably longer than the 1 to 2 hours duration of naloxone.[35] Frequently, naloxone must be repeated every hour or two to maintain the awake state. Deleterious effects of overdosage with naloxone include nausea, vomiting, excessive arousal, excitement, and pain following a surgical incision, some of which may be due to sudden arousal at a high P_aCO_2. If excessive dosage or sensitivity to barbiturates results in postanesthetic hypercarbia, it can be countered with doxapram 1 mg per kg. However, we try to avoid analeptic agents and allow awakening to occur naturally with time. In patients with hypercarbia from residual anesthesia, removing the endotracheal tube reduces a major stimulus for arousal. Such a patient may return to an anesthetized state after extubation. Thus one must look for additional signs of emergence other than a response to the endotracheal tube.

If hypercarbia is related to inadequate mechanics of respiration, it is usually caused by excessive pain from the surgical incision or by neuromuscular blockade from muscle relaxants[11] – with or without residual anesthesia. The latter can be treated by properly monitoring neuromuscular function and reversing the muscle relaxant. Excessive pain can be treated with either nerve blocks or small intravenous doses of narcotics, e.g., 1 to 3 mg of morphine sulfate intravenously.

When hypercarbia results from *intrapulmonary disease,* knowledge of the pre-existing parenchymal problem is necessary. Baseline preoperative pulmonary function and blood gas measurements help determine the level of expected recovery. This patient is often intubated and ventilated postoperatively because of his chronic lung disease. However, early removal of the endotracheal tube may be indicated to reduce bronchospasm from the foreign body stimulus of the tube itself. This will improve coughing and mobilize secretions. The decision to extubate depends on (1) the disease process, (2) intrinsic respiratory drive, and (3) patient cooperation.

Hypoxemia

Postoperative hypoxemia is a common occurrence which has been reviewed in detail.[37, 44, 53] *Room air breathing* (F_iO_2 0.21) is insufficient for many patients following anesthesia because of increased physiologic shunt,[12] decreased compliance,[60] airway closure,[19] pulmonary edema, lung collapse from intubation of a mainstem bronchus,[28] pneumonia, an extensive body cast, thoracic or abdominal surgery,[3, 12] posture,[18] or pre-existing disease. Ventilation/perfusion abnormalities are usually observed in the elderly patient[32] or in one with chronic obstructive pulmonary disease or pulmonary vascular disease. *Hypoventilation* can also lead to hypoxemia.

Increased oxygen consumption occurs postoperatively from fever, shivering, disorientation and restlessness, seizures, peritonitis, and hyperthyroidism. *Decreased cardiac output*—stemming from arrhythmias, depression of myocardial contractility, hypovolemia, increased peripheral vascular resistance from hypothermia, and increased pulmonary vascular resistance—results in less fully saturated blood returning to the pulmonary vasculature, magnifying any currently existing shunt.[47] The diagnosis of hypoxemia can rarely be made clinically until desaturation becomes extreme. Measurement of arterial P_{O_2} (preferably on 100 per cent oxygen to obtain an alveolar-arterial oxygen gradient) provides the most clinically useful information.

Clinical signs of hypoxemia are variable and include hypertension, hypotension, tachycardia, bradycardia, cardiac arrhythmias, dyspnea, tachypnea, or hypoventilation. There may also be central nervous system depression or disorientation with agitation. Cyanosis is not a reliable sign of hypoxemia. Fluorescent lighting can alter the ability to detect cyanosis, and anesthetic effects on cutaneous vasomotor control can render the interpretation of skin color and perfusion inaccurate.[16] In vasoconstriction there can be cyanosis peripherally in spite of high P_aO_2. Circulatory and respiratory responses to hypoxemia are modified by anesthesia.[15] Sick patients still influenced by anesthesia may not respond to a hypoxemic stress by hyperventilating and increasing cardiac output, but instead develop cardiorespiratory depression and its sequelae. After bilateral carotid thromboendarterectomy, the patient may lose his hypoxic response entirely.[58]

Oxygen therapy does not eliminate the cause of hypoxemia but may symptomatically alleviate it[23] while concomitant measures are employed to relieve the cause itself. If related to *hypoventilation* from excessive anesthesia or inadequately reversed muscle relaxants, immediate correction is indicated. *Ventilation/perfusion* abnormalities improve with good chest physiotherapy, deep breathing and a stir-up regime. Rapid emergence from general anesthesia will encourage early patient cooperation.

Cardiac output will increase with appropriate volume and drug therapy. Myocardial depression is frequently the consequence, rather than the cause, of hypoxemia. Reduction of peripheral vascular resistance and improvement in tissue perfusion occur as the patient warms. When indicated, skin perfusion can be improved with small doses of ganglionic or alpha adrenergic blocking agents. These are useful if the patient is already hypertensive. Normally, cardiac output should increase in response to increased oxygen consumption. However, due to residual anesthetic depression, this may not occur and inotropic agents may be temporarily required.

Indications for oxygen enrichment postoperatively are very general. Essentially every patient demonstrates a reduction in P_aO_2 following general anesthesia[6, 37, 44] and can benefit from oxygen administration. Because long-term utilization is not anticipated, problems of oxygen toxicity are irrelevant.

One oft-mentioned complication of oxygen therapy is respiratory depression in the chronically hypercarbic patient with an hypoxic drive. In the past, this concept has been grossly exaggerated when applied to the postoperative patient. Specifically, oxygen should never be withheld for fear of reducing or abolishing an hypoxic drive. In the presence of mild respiratory depression from chronic obstructive pulmonary disease, graded doses of oxygen can be administered from a Venturi mask while following the patient with blood gas determinations. Respiratory depression or severe hypercarbia are detectable with close observation. If either of these develop, the patient should be intubated, ventilated, and oxygenated.

Postoperative Ventilatory Care

As methods for respiratory care improve, indications for postoperative ventilation are being increasingly liberalized. In the elderly, the ratio of closing volume to functional residual capacity increases, elastic recoil diminishes, and atelectasis occurs more frequently. Narcotic analgesia, restrictive binders of the abdomen and chest, abdominal distention, obesity, and incisional pain lead to ventilation/perfusion abnormalities. Changes in circulating volume, electrolyte imbalance, extensive surgical dissection, hypothermia, and state of consciousness lead indirectly to ventilatory inadequacy. A patient exhibiting these problems following anesthesia and surgery should be ventilated for some pre-set time while the deranged organ systems return to and maintain reasonably normal preoperative function. Close monitoring and evaluation of directional changes are crucial. Rather than placing the burden of proof upon the patient to demonstrate his need for intubation and ventilation, the physician must demonstrate that these measures are unnecessary. The responsibility thus shifts from patient to physician.

The principle of continuing intraoperative respiratory support into the postoperative period allows all other systems to function in an environment of normoxia, normocarbia, and normal pH. Since many postoperative problems are the direct result of deficiencies in oxygenation, CO_2 elimination, electrolyte and acid-base balance, these particular stresses should be prevented while other systems recover. In most instances, an evaluation can be determined intraoperatively and the patient extubated immediately. However, hours or even days of ventilatory support may be indicated. Since these decisions must be individualized, no hard and fast rules exist; but if the general approach is staged, a logical order of steps leading to safe recovery will follow.

PULMONARY SECRETIONS. Coughing is essential for clearing airway secretions. However, the supine position, residual anesthesia, pain on inspiration or with forced expiration render it ineffective. Methods to stimulate deep breathing include administration of 5 per cent CO_2, re-breathing tubes, blow bottles, blow gloves, or intermittent positive pressure breathing. In a patient with intact airway reflexes, tracheal suction will stimulate involuntary coughing. Injecting saline directly into the trachea or through a percutaneous transtracheal catheter stimulates coughing and thins secretions so they are more easily raised. When excellent chest physiotherapy is available, these treatments are rarely, if ever, needed.

ASPIRATION PNEUMONIA. Vomiting and aspiration during or following anesthesia and surgery are fearful hazards.[1] A patient with a full stomach receiving general anesthesia requires an endotracheal tube until he is fully awake and demonstrating control of his own airway. Similarly the patient with an incompetent cardioesophageal junction or esophageal stricture is vulnerable to regurgitation and aspiration even if he was "NPO" preoperatively. Although an elective patient is "NPO" many hours prior to surgery, retention of gastric secretions can promote regurgitation or vomiting of large amounts of gastric material. Since another cause of vomiting is excessive airway and pharyngeal stimulation from the endotracheal tube or oropharyngeal airway, their removal could deter vomiting. The problem is paradoxical: precisely that mode of therapy which prevents aspiration from vomitus also serves to initiate vomiting. In the elective "NPO" situation, expert clinical judgment is necessary to assess the optimal time for extubation. The maxillofacial surgery patient is a case in point. Until fully awakened, a patient whose jaws have been wired shut or closed with rubber bands requires a cuffed nasotracheal tube. The probability of aspiration after vomiting is very high in the presence of wires or bands, even if released quickly.

When vomiting occurs, the patient should be turned on his side with the head down steeply, allowing material to drain out of the mouth. The airway can then be thoroughly cleared with suction.

When aspiration is suspected, investigation and treatment should be implemented without delay. The pH has prognostic value because acidic vomitus (pH less than 2) presents a much more grave threat of chemical pneumonitis than aspiration of a similar volume with a pH of 5 or 6. The lungs must be examined frequently for evidence of pneumonitis manifested by wheezes, rhonchi, and rales. A chest x-ray and arterial blood sample for measurement of P_aO_2, P_aCO_2, and

pH must be immediately obtained. Each of these serves as a baseline if changes develop.

Many patients can be treated conservatively without difficulty, but the occasional patient will develop acute respiratory failure requiring all supportive means pertinent to the care of the critically ill patient.[2]

CARDIOVASCULAR COMPLICATIONS

Hypotension

Postoperative hypotension is very common and requires immediate investigation. Before any therapy is instituted, the following need to be checked quickly: artifactual measurement due to an improperly placed or sized blood pressure cuff, possible error in blood pressure measurement,[37] the differential between one extremity and the other, or miscalibration of a transducer.[14, 26, 40] Clinical signs of hypotension and hypovolemia include: (1) color—pale or gray; (2) skin—cold, clammy, diaphoretic; (3) pulse—rapid, thready; (4) respiration—rapid and shallow; (5) cerebral ischemia—disorientation, restlessness, anxiety. However, it is often difficult to recognize these signs because they are modified or completely abolished by residual anesthesia. Cutaneous vasoconstriction may not occur to diminish skin color; diaphoresis may be absent in the face of sympathetic blockade; a weak pulse may be slow, not rapid; respirations may be shallow and slow; and central nervous system signs of ischemia may be altered.

Therapy for hypotension includes: administration of fluid, reversal of anesthetic depressants, and treatment of arrhythmias and bradycardia. A vasopressor or positive inotropic agent is occasionally used to raise blood pressure and prevent coronary hypoperfusion.[27] The patient can autotransfuse about 2 units of blood when he is properly positioned with his legs flexed at the pelvis. Vagal tone is frequently elevated from painful stimuli, previous traction reflexes, or high spinal anesthesia possibly manifesting bradycardia and hypotension. Intravenous atropine in 0.5 mg increments may be useful to block these reflexes. If hypotension persists in spite of early and simple therapy, myocardial infarction or pulmonary embolism should be suspected.

Arrhythmias

Serious arrhythmias are observed during recovery from surgery and anesthesia.[9, 31, 45] Many of these both develop and revert spontaneously. However, a significant arrhythmia cannot be ignored, particularly if myocardial function is impaired.

TACHYARRHYTHMIAS. Sinus tachycardia is often due to pain, hypertension, fluid overload, hypovolemia, congestive heart failure, emergence excitement, hypoxemia, hypercarbia, excessive atropine administration, and residual gallamine or pancuronium effect.

Premature ventricular contractions (PVC's) commonly occur postoperatively. Their potential danger depends on their proximity to the T-wave of the previous beat. Frequently PVC's convert into bigeminy, trigeminy, or quadrigeminy. This may be followed by ventricular tachycardia which can progress to ventricular fibrillation.[61] PVC's often signify organic heart disease, but they are also seen in the patient with no previous history or electrocardiographic evidence of heart disease. Bradycardia associated with ventricular escape beats, hypertension, metabolic or respiratory alkalosis, and hypokalemia (especially in the digitalized patient[17]) increases the patient's susceptibility to PVC's, and these precipitating factors should be ruled out. In addition, sympathetic stimulation from hypoxemia, hypercarbia and pain predisposes a patient to PVC's. Because hypokalemia is so commonly found postoperatively[16] and contributes to PVC's, it is necessary to deal with this cause of ventricular arrhythmia before proceeding further. Respiratory alkalosis further augments hypokalemia. In addition, the patient who receives massive blood transfusion may develop significant hypokalemia, although the reason remains obscure. Gastric lavage for upper gastrointestinal bleeding washes out hydrogen, potassium, and chloride ions.

Ventricular arrhythmias are particularly worrisome in the digitalized patient. A new 12-lead EKG should be compared to the preoperative EKG to determine the unifocal or multifocal nature of the PVC, its relationship to the T-wave, and the presence of myocardial ischemia or infarction. Blood gases should be checked for abnormalities which can initiate PVC's. A central venous catheter erroneously passed into the right ventricle may also cause ventricular arrhythmias. Preoperative medications – particularly digitalis – and the anesthetic administered must be noted. When hypokalemia is suspected, while awaiting the results of the serum potassium level, lidocaine may be injected intravenously up to a total of 5 mg per kg in 50 mg boluses every 3 to 5 minutes.[5] If the serum potassium is less than 3.5 mEq per L, potassium may be supplemented.[55] If it is more than 4.5 mEq per L, reliance is placed on a lidocaine infusion. Further therapy includes procainamide, or diphenylhydantoin. The latter is thought by some to be particularly useful for digitalis-induced arrhythmias.[38] Finally, if these measures fail, propranolol 0.5 to 1.0 mg intravenously in incremental doses will reduce the frequency of the PVC's. Atropine is useful when PVC's represent escape beats from a slow sinus heart rate. If PVC's develop into ventricular tachycardia, cardioversion is beneficial.

BRADYARRHYTHMIAS. Sinus bradycardia is usually due to high sympathetic blockade from spinal anesthesia or to excess acetylcholine from the anticholinesterase drugs used to reverse neuromuscular blockade. It can also be associated with abnormal reactions to pain, gastric dilatation, increased intracranial pressure and a distended bladder. Treatment of the precipitating cause and the use of atropine may raise the ventricular rate to an appropriate level; however, larger doses of atropine may precipitate ventricular fibrillation.[39]

Nodal arrhythmias are often encountered during anesthesia and may carry over into the postoperative period. These usually revert upon awakening or after administering atropine.

Acute Pulmonary Edema

Acute pulmonary edema manifested by tachypnea, respiratory distress, tachycardia, hypo- or hypertension, and peripheral vasoconstriction occasionally develops early in the postoperative course.[13] Auscultation reveals wheezes, rales, and/or rhonchi and often the presence of a third heart sound. A chest x-ray usually demonstrates increased vascular markings and bilateral infiltrates radiating from the hilum. If the patient has been in the lateral position intraoperatively, unilateral pulmonary edema may occur. However, because the patient is still under the influence of residual anesthesia, the typical signs are often unrecognized until very late in the postoperative course.

In the operating room, volume overload occurs easily with shifts in extracellular fluid volume. In order to prevent intraoperative hypotension, fluid administration may be large. As the anesthetic wears off, vasoconstriction increases venous return. A diseased heart may not be able to adequately handle this load. This same mechanism may hold true when spinal or peridural anesthesia wears off. Other causes of left ventricular failure-pulmonary edema include severe hypertension from pain, hypothermia, hypercarbia, hypoxemia, and acute myocardial infarction.

A second major physiologic insult leading to pulmonary edema is altered capillary permeability.[50] Many events inciting this condition have been suggested, including release of vasoactive substances or endotoxins; disseminated intravascular coagulopathy; drug reactions;[56] aspiration pneumonia; smoke inhalation following major burns; the pulmonary effects of trauma; and inhalation of toxic agents such as phosgene or nitrogen oxides.

Following head trauma or intracranial surgery, the neurosurgical patient is susceptible to central sympathetic discharge resulting in left ventricular failure and "neurogenic pulmonary edema."[20, 36]

Therapy for acute pulmonary edema depends on the pathophysiologic insult. If left ventricular failure is responsible, left atrial pressure and afterload must be reduced. The patient should be placed in semi-Fowler's position, oxygen administered to relieve hypoxemia, and small doses of intravenous morphine administered to alleviate anxiety and promote peripheral venodilatation. Furosemide 20 to 40 mg intravenously induces acute and often profound diuresis requiring

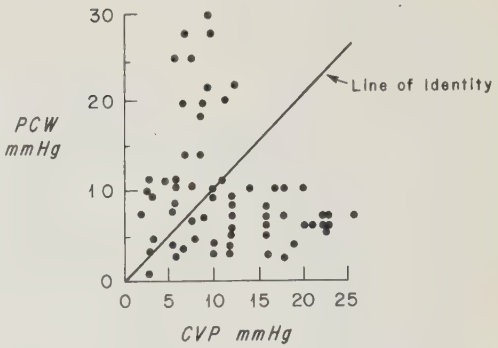

Figure 1. In critically ill surgical patients, central venous pressure correlates poorly with pulmonary capillary wedge pressure under a wide variety of circumstances. The straight line represents the line of identity. These individual data points represent actual measurements obtained in surgical patients. (Adapted from Civetta, J. M., and Gabel, J. C.: Flow directed pulmonary artery catheterization in surgical patients: Indications for modification of technique. Ann. Surg. *176*:753–756, 1972. *And* Toussaint, G. P. M., Burgess, J. H., and Hamson, L. G.: Central venous pressure and pulmonary wedge pressure in critical surgical illness. Arch. Surg., *109*:265–269, 1974.)

monitoring of serum potassium. Although one may assume that the patient in acute pulmonary edema needs inotropic support, its etiology should be determined before administering digitalis. When central venous pressure is very high, and tachycardia and oliguria are accompanied by a reduced cardiac output, acute digitalization or inotropic support is beneficial. If central venous pressure is low, pulmonary edema may be caused by isolated left ventricular failure or by capillary permeability without either left or right ventricular failure.[50] In this situation, insertion of a pulmonary artery catheter more accurately differentiates left ventricular from right ventricular filling pressures[25] (Fig. 1). The patient with acute pulmonary edema may also be hypovolemic because of volume lost into the lung. Precise monitoring of ongoing volume and inotropic therapy is easier with pulmonary capillary wedge pressure measurement.

Determining arterial Po_2, Pco_2, and pH is essential when oxygenation is seriously impaired or when laborious breathing induces fatigue and CO_2 retention. Acute pulmonary edema is not an automatic indication for intubation and ventilation. Fluid overload, the most common cause of pulmonary edema, can often be managed conservatively. However, for most other causes of acute severe pulmonary edema—particularly after intraoperative myocardial infarction or from altered capillary permeability—positive pressure ventilation is essential to insure adequate oxygenation and CO_2 removal.

Temporary improvement of myocardial contractility is achieved with isoproterenol or dopamine. However, this is often followed by tachycardia and irritability which may adversely affect the patient with myocardial infarction. Furthermore, recent evidence suggests that isoproterenol could be contraindicated in the patient with acute myocardial infarction because of increased myocardial work and myocardial oxygen consumption.[27]

METABOLIC COMPLICATIONS

Hyperkalemia

Hyperkalemia is observed with chronic renal disease or abnormal administration of potassium but only rarely after massive blood transfusion.[51] Hyperkalemia is usually diagnosed by serum potassium measurements and occasionally by the characteristic electrocardiographic picture of peaked T-waves, depressed ST segments, and prolonged QRS interval. Immediate treatment includes hyperventilation, intravenous administration of 1 gm calcium chloride, one or two ampules of sodium bicarbonate, or 50 ml of 50 per cent glucose with 10 units of insulin. Long-term management involves administration of sodium-cycled Kayexalate resin for ion exchange and hemo- or peritoneal dialysis.

Hypothermia

Most patients returning from air-conditioned operating rooms are hypothermic, particularly following prolonged procedures and extensive dissection.[42] Since the one factor most responsible for hypothermia is operating room temperature, any level below 21° C (70° F) prevents maintenance of normothermia (Fig. 2). A hypothermic patient is intensely vasoconstricted, which results in impaired peripheral perfusion, metabolic acidosis, and, frequently, hypertension. Hypovolemia is masked but becomes apparent upon rewarming, making volume replacement with proper monitoring mandatory.

Postanesthetic shivering is commonly experienced on emergence from general anesthesia.[19] Oxygen consumption and CO_2 production are elevated when the patient is least equipped to increase oxygen delivery to the tissues and CO_2 elimination. Cardiac output must increase to satisfy tissue oxygen demand, yet may be prevented from so doing by residual anesthetic depression. Moreover, cardiac output might increase but at great expense to myocardial oxygen consumption and myocardial work. In a patient with coronary artery disease, myocardial overwork can lead to infarction. In a hypothermic patient stressed by volume and circulatory derangement, poor respiratory function should be aided by ventilatory support until normothermia is achieved.

If significant hypertension and cutaneous vasoconstriction exist, pharmacologic vasodilatation can temporarily increase cutaneous blood flow, allowing surface warming to progress more rapidly. Covering vasoconstricted skin with warm blankets accomplishes little, except to provide comfort. When hypothermia co-exists with hypertension, trimethaphan may reduce blood pressure and vasodilate the peripheral vessels. Although intravenous thorazine or droperidol is useful, each is long-acting and less readily reversible. Oxygen administration is essential. Measurement of arterial Po_2, Pco_2, and pH monitors the degree to which hypothermia and shivering interfere with oxygenation, CO_2 elimination, and acid-base balance.

Postoperative Pain and Emergence Delirium

The incidence and severity of postoperative pain are so variable that the approach to each patient must be individualized. Generalizations about drug therapy are useless. Preoperative psychologic preparation is extremely helpful in reducing the need for postoperative analgesia.[22] But the mental state of the patient and site of operation both contribute to the degree of relief required for postoperative pain. Since so many analgesic methods are touted as being effective, obviously none is universally accepted.[7, 8, 43] Morphine sulfate (1 to 3 mg intravenously) gives satisfactory analgesia in the recovery room. Some physicians

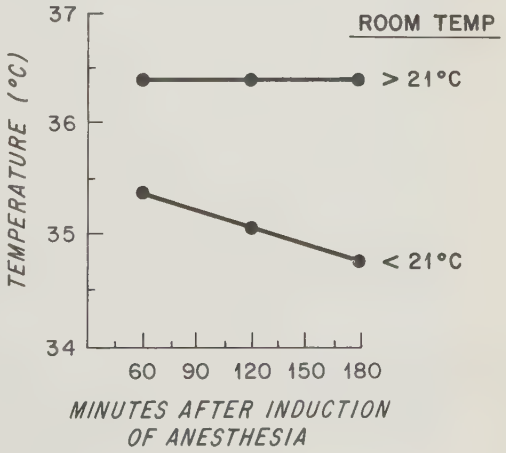

Figure 2. When room temperature falls below 21°C, esophageal or nasopharyngeal temperature decreases gradually with time. Maintaining room temperature above 21°C allowed body temperature to remain constant within normal limits. (Adapted from Morris, R. H., et al.: The effects of ambient temperature on patient temperature during surgery not involving body cavities. Anesthesiology, 32:102–107, 1970.

prefer shorter-acting narcotics such as fentanyl 0.05 mg intravenously. In the first 24 hours following anesthesia, lower than usual intramuscular doses will mitigate the problem of synergism and excessive respiratory depression. Two regional blocks recommended for pain relief are thoracic epidural anesthesia and continuous intercostal block.[1] Recent introduction of the long-acting local anesthetic, bupivacaine, makes the above techniques more attractive.[8]

Excitement following emergence from general anesthesia is displayed particularly by the younger patient who, lacking analgesia, may be difficult to control. After ruling out hypoxia, hypercarbia, or cerebral ischemia, this excitement can be treated with small doses of intravenous narcotics. Emergence delirium occurs more frequently after scopolamine premedication than after atropine, especially when scopolamine is administered without a narcotic.[21] Physostigmine (1 to 3 mg intravenously) may succeed in reversing scopolamine-induced delirium.[52]

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The Chronic Pain Syndrome

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> And a certain woman... had suffered many things of many physicians and had spent all that she had, and was nothing better, but rather grew worse.
>
> MARK 5:25

Pain in one form or another is the most common reason a patient decides to consult a health care professional. Nevertheless, the suffering experienced in relation to pain remains a poorly understood and frequently mismanaged phenomenon. The word 'pain' itself may have many different meanings, ranging from an expression of the acute discomfort resulting from an abscessed tooth to the mildest of a child's imagined hurt; or from the most profound of religious ecstacies to a mild statement of irritation that a companion is "a pain in the neck."[11]

Many definitions have been attempted from "Pain is that which hurts" to Sternbach's relativistic definition, "'Pain' is an abstract concept, which an observer may use to describe: (1) a personal, private sensation of hurt, (2) a harmful stimulus which signals current or impending tissue damage, or (3) a pattern of responses which operate to protect the organism from harm."[18] More psychologically, Melzack suggests that pain may be defined in terms of a multidimensional space comprising several sensory and affective dimensions. He proceeds to make a substantial contribution concerning the language used to describe pain.[13, 14] In a more philosophical sense, C. S. Lewis states "Pain is any experience whether physical or mental which the patient dislikes."[10] A most acceptable contemporary working definition of pain is that proposed by Merskey. Pain is "an unpleasant experience which we primarily associate with tissue damage, or describe in terms of tissue damage, or both."[15] This definition combines the subjective experience, an apparent physical pain generator, and the responses by which another observer would agree that one was in pain.

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Supported in part by USPHS Grant GM 15991.

Another distinction must be made when discussing pain: the difference between acute pain and chronic pain. All too often both the physician's and the patient's experience with acute pain is carried over into the area of chronic pain with disastrous results. Thus the patient with long-standing low back pain, certain headache states, or multiple diffuse myofascial complaints is treated with drugs and surgery as an acute pain patient might be treated; but instead of the relief expected the patient becomes worse. Both treator and treatee become desperate seeking out stronger medications and more mutilating surgeries until each regards the other as being incompetent or psychologically disturbed. It is to a better understanding of this problem of chronic pain that we must direct ourselves.

CHARACTERISTICS OF THE CHRONIC PAIN SYNDROME

The constellation of symptoms accompanying the patient with chronic pain is characteristic enough to constitute a disease entity we shall call the "chronic pain syndrome" or CPS. Pain, illness, or environmental changes must be present for about 6 months to establish this condition.[20] The victim of CPS suffers from intractable, often multiple, pain complaints, which are usually inappropriate to existing somatogenic problems; multiple physician contacts and many nonproductive diagnostic procedures; excessive preoccupation with the pain problem; an altered behavior pattern with some of the features of depression, anxiety, and neuroticism, and, in particular, no realistic plans for the distant future. This syndrome in its later stages is accompanied by excessive use of analgesic medications and multiple surgical procedures, often demonstrating no clear organ pathology.

Chronic pain leads its victim to despair at the seeming uselessness and endlessness of this suffering. Sleep patterns are altered suggesting a primary disturbance of the circadian rhythm. Progressive physical and mental disability follow. Since pain is an acceptable affliction in our society and one especially worthy of sympathy, friends and family may act to sustain or even increase invalid behaviors by their well-meaning attention.

The chronic pain patient in his search for help is exposed to the high risk of iatrogenic complications at the hands of well-meaning physicians.[4] These physicians are not malicious, but are practicing exactly as they have been trained. Analgesic abuse, including narcotic addiction, is common in the CPS since physicians who have been taught the proper use of these medications for acute pain and have confirmed their efficacy in this area, apply the same therapy to the CPS. Unfortunately, long-term use of analgesics for chronic problems will result in addiction and an increase in reported pain intensity.[20]

If the patient afflicted with the CPS seeks out the assistance of a surgeon in solving his pain problem, surgery is a likely consequence. This may first consist of diagnostic and corrective surgery, such as laparotomies, laminectomies, or discectomies. Later, when the pain has

failed more direct treatment, surgery may be done directly on the nervous system to cut pain pathways, implant stimulators or alter behavior. It is a tribute to the organization of the human nervous system that it is able to successfully negate all these attempts at pain relief within 6 months to several years. Unfortunately, many patients with CPS have had 10 to 20 procedures and some over 30 or 40.

Some patients with CPS, in a frantic desperate search for help, turn to quackery. For those with benign problems, this is a fortunate choice since they come to no harm through strong medications or surgery. They pay at most a financial price. Unfortunately while they recieve the necessary attention and laying on of hands to satisfy their emotional needs, a thorough medical and psychiatric exam is lacking to rule out any more serious or directly treatable disease. Thus, this route is not to be recommended.

Chronic pain is a national disease of major importance resulting in a loss of work productivity as well as the more direct costs of medical, hospital, and compensation services. For example, in 1971, the cost of low back pain to the people of California was $200 million.[5] This social and economic stress both affects the family directly and drains the limited resources of our national health care systems.

Another way of viewing the problem of the patients suffering from CPS is to consider them as individual failures of an efficient health care delivery system. The health care system increases the physician's efficiency, thereby permitting him to treat more patients in less time at a lower cost. Unfortunately, inherent in this is a reduction of physician-patient contact time. A certain percentage of patients, those with more obscure problems, such as multisystem disease or psychogenic overlay, do not respond to this approach and begin seeing other physicians. This help-seeking behavior becomes more desperate and yet more stereotyped and nonproductive. It is obvious that more of the same, whether it be physician contact, medications, or surgery, is not going to help. A new and different approach, such as that offered by a multidisciplinary pain clinic or a sensitive physician skilled in management of the CPS, is necessary.[3]

MANAGEMENT OF THE PATIENT WITH CHRONIC PAIN SYNDROME

As with any medical problem, a proper diagnosis is essential before proceeding with therapy. A diagnosis is often particularly difficult in these patients since, unfortunately, most patients with a chronic pain syndrome come with an established diagnosis. This may be a diagnosis established by exclusion or may be so outdated as to be useless. More often it is a description of a disease rather than a cause of the patient's pain and suffering. It is frequently necessary, even in the face of an established diagnosis, to clearly find out the cause of the patient's pain problem. This principle is most flagrantly violated in patients with a diagnosis of inoperable cancer. If this label is accepted, the therapy that

follows is often too early use of strong narcotic analgesics on a "prn" basis. Thus the physician ignores the fact that the patient's pain complaints really represent his expressions of fear, depression, and anxiety, all better treated with psychotropic drugs and sympathy. It is notable that most cancer patients do not have pain until they are made aware of their disease.[23] Their suffering is a reasonable response to an appropriate severe anxiety reaction.

By the time the chronic pain syndrome has been identified, it has already proved resistant to management by the usually efficient, conventional medical approaches. Therefore, a novel and necessarily more time consuming approach to diagnosis and treatment is necessary. One such approach is that offered by the multidisciplinary pain clinic.[3] The management philosophy outlined here is that followed in the multidisciplinary diagnostic pain clinic at the University of Washington which operates according to the principles established by Dr. John J. Bonica and others.[3, 4, 17, 21] While these principles operate best in a large university hospital setting, they may nevertheless be readily applied in a small group practice or, in less complex cases, in an individual's private practice if the physician is so inclined.

A physician undertaking the primary management of a patient with a chronic pain syndrome must first decide, if he has the resources, that he is willing to manage this type of patient. The physician and his team may expect to become the focus of the patient's, and his family's, hostility, anger, and manipulations. These patients will prove more stressful to the physician than most other patients. Financial rewards will also be minimal since many third party carriers are not willing to pay for special services required by this type of patient even if they may receive a long-term benefit. Procedures, not time, are paid for and considerably more time must be spent in management of patients with CPS.

If a physician undertakes the care of a patient with CPS, he should first understand that conventional medical evaluation is unlikely to succeed. Conventional medical evaluation proceeds through functional inquiry, physical examinations, and laboratory procedures to a physical diagnosis. If a clear diagnosis is not forthcoming and complaint persists, therapy is nevertheless applied. At first, this therapy may be conservative but because of the persisting nature of the complants, more and more serious measures will be taken. The type of therapy to be received is all too often determined by the patient through his selection of his physician. If he repeatedly knocks on surgeons' doors, he is bound to receive surgery. If he knocks repeatedly on internists' doors, he will receive strong analgesic medication. The patient may finally be told "the pain is in your head," and he is sent to a psychiatrist whom he meets with surprise and hostility. The patient interprets this referral to mean the doctors think he is crazy, which unfortunately is not as acceptable as being physically sick.

In contrast to the conventional approach, a multidisciplinary pain clinic work-up commences with simultaneous evaluation of the factors affecting the patient physically, mentally, and environmentally. It is explained to the patient that these factors interrelate and must all be

thoroughly evaluated to understand his problem. Participation of the spouse is essential and the patient's manager in the pain clinic must be free to contact any outside physician the patient has seen. If the patient is not agreeable to these terms, it is obvious that he does not want help at this time and he should be duly dismissed from the clinic until he is ready to cooperate in his own care.

During the initial interview with the patient and spouse, the plans for evaluation are explained in detail. Thus is a sound physician-patient relationship established. Legal releases for information from outside physicians are filled out and all pertinent past medical records, operative reports, and x-rays are collected. Identification of all physicians currently treating the patient must be made and permission obtained to communicate with them concerning the patient's problem. Many of these physicians will be minor contacts used by the patient only to obtain analgesic medication. Litigation or compensation must be directly inquired about since they have a significant influence and frequently are not admitted to until later.[16]

A medication abuse problem may be directly admitted to by the patient or his wife or revealed by the patient's speech and actions. If any suspicion of such a problem exists, this must be investigated before further management of the patient can be undertaken. This is such a significant factor in the chronic pain syndrome that a following section is devoted to it.

In a large group practice individual patients often lose the opportunity to establish a close relation with an individual physician. To avoid this, in the pain clinic each patient is assigned an individual physician as his manager. This physician has the responsibility for the initial examination of the patient and for deciding to which consultants the patient should be referred. He also acts as a liaison between the patient, the patient's referring physician, and the rest of the pain clinic group. If the patient is to be presented in a pain clinic conference, the manager circulates the summary of the patient's work-up, and after the conference relays the recommendations of that group to the patient, the patient's family, and the referring physician.

In addition to the traditional functional inquiry and physical examination, a very thorough and detailed history and description of the pain problem is obtained. Some of this evaluation involves forms such as a 2-week diary filled in prior to coming to the clinic, so that detailed chronology of the pain behavior may be noted as well as the level of activity. Activity is best characterized by the number of hours the patient is up, as opposed to the number of hours the patient is at rest. The actual up time and down time as measured by the diary method may bear no relation to the patient's complaints and often gives an insight into the real magnitude of the disability. Evaluation of the mental status is assisted by the Minnesota Multiphasic Personality Inventory and the Zung depression scale as well as by the impressions obtained by the managing physician, a psychiatrist, and a clinical psychologist. Environmental factors are assessed by questionnaires designed to detect stresses at work and in the home. A social worker is useful in assessing economic and other stresses in the environment.

Most important in the management of the chronic pain patient is the regular face to face confrontation of all the health care professionals taking care of the patient. This type of discussion, whether one to one or in a group, is much more effective and productive in making a correct diagnosis and formulating the appropriate therapeutic strategies than communication by letter or telephone or through the fragmented independent efforts inherent in traditional medical practice. In addition to the service provided in the management of the individual patient, these conferences serve as an excellent forum for the exchange of ideas and information and constitute a highly effective teaching mechanism.

In summary, the methods used to establish a working diagnosis in the patient with chronic pain syndrome are those of conventional medical practice; perhaps more compulsively applied and including at the same time thorough psychologic and environmental assessment. Equal acceptance of all members of the health care team and their direct face to face communication is a single most essential feature in management of the chronic pain syndrome. This approach to the patient is time-consuming but since the unfortunate patient with CPS will get more than his share of time out of the Health Care System in any case, it is better that it be structured time leading to appropriate therapy.

MANAGEMENT OF THE ABUSE OF ANALGESIC MEDICATIONS

Abuse of analgesic medications is the primary factor sustaining ill behavior in over 50 per cent of patients presenting with CPS. Its detection and efficient management is therefore of prime importance. No responsible physician would attempt to diagnose or treat a patient for a long-standing illness if the patient were to come into his office drunk. Yet the same physician may make a diagnosis leading to a prescription for a strong medication or even surgery on a patient who came into his office under the influence of large amounts of analgesic medications. Confusion of higher thought processes, similar to drunkeness, which results from continued use of prescription analgesics is ignored by most physicians even though it may contribute to misdiagnosis and inappropriate therapy. Chronic users of analgesic medications report less pain after these medications are discontinued.[20] So important, and sometimes subtle, is this problem that a basic principle in the management of pain patients is that whenever excessive, or chronic use of medication is even suspected it must be cleared up before a meaningful diagnostic evaluation can be attempted.

A medication problem should be suspected when a patient appears depressed, has slurring of speech, documents an abnormally high down time on the 24 hour diary, is too conversant about the names of drugs, or complains of constipation. Medication administered parenterally, either in the neighborhood emergency room or at home, is an indication of a medication problem.

Short-acting analgesics are often taken to excess in a cyclic fashion because of their side effects, which produce a subjective sensation as-

sociated with protection from pain and a feeling of detachment from the responsibilities of the world. These lead to at least a psychologic dependence on pain medication. Pain, either verbalized or acted out, is the stimulus to the environment that evokes more drugs in a socially acceptable manner (Fig. 1).

Patients with medication problems must be managed on an inpatient basis with goals of assessing the magnitude of the abuse, controlling medication intake, and then effecting a smooth withdrawal. The informed consent of the patient and spouse is necessary. Both must accept that this is indeed a problem. The patient comes to the hospital with all of his current medications and is admitted. The medications are turned over to the ward nurse. The patient's belongings are searched for concealed medications. Perhaps through fear of suffering, it is characteristic of these patients to secrete medications. It is a sign of confidence in the program when, later, they voluntarily give up, or admit to having used, their hidden stores. The patient's spouse is urged to destroy any medications and prescriptions remaining at home. A Drug Profile routine is begun on admission to hospital.

The drug profile is intended to give an indication of the type and quantity of medication needed by the patient (Fig. 2*a*). This is accomplished by placing the patient in a closed environment, the hospital, and letting him have whatever medication he requests. The ward staff administers the medication and keeps a careful record. This has proven to be safe in the type of patient described here and rapidly gives an insight into the nature and magnitude of his medication problem. At the end of 24 hours, or, if the situation is not clear, at the end of 48 hours, the type,

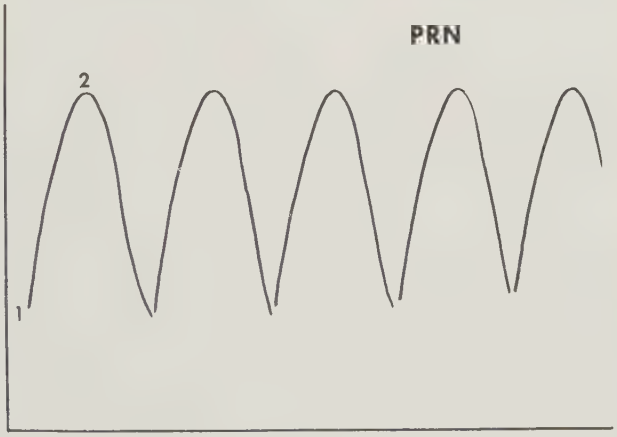

Figure 1. *Cyclic effects of short-acting analgesics.* The ordinate is the level of analgesic, the abscissa is time in units of 2 to 3 hours per cycle. At point *1* a short-acting analgesic is administered. Soon after, an inappropriately high level of analgesic is established, producing a side effect on the higher centers. Because of this the patient, now at point 2, has what may be described as a "two martini feeling." The worries of the world are gone and the subject withdraws into himself in a carefree, guiltless fugue state, like the classic Lotus Eaters: "Surely, surely, slumber is more sweet than toil."[22] Soon, however, this effect wears off. Characteristically the victim of CPS, in preference to re-entering the real world, repeats his trip. The "fix" necessary for the trip is obtained by the socially acceptable expression of pain and thus the cycle repeats.

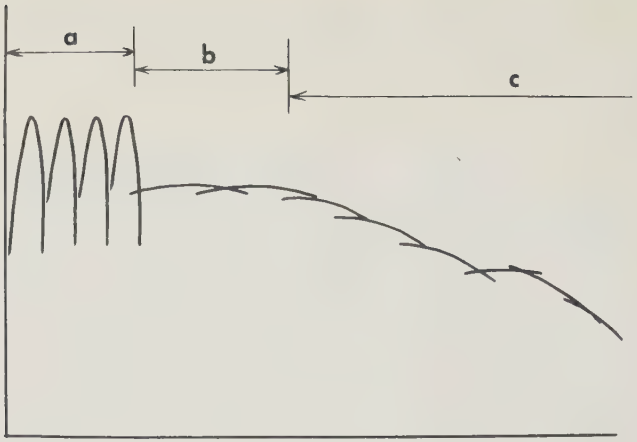

Figure 2. *Medication assessment, control, and withdrawal.* Coordinates are as in Figure 1. *a*, Period of Drug Profile to assess physiologic dependence on medications. *b*, Period of medication control with patient receiving 100 to 120 per cent equivalent of long-acting analgesic agents. *c*, Time of withdrawal at the rate of 10 to 15 per cent per day for narcotics, and 5 to 10 per cent per day for barbiturates. Medication levels are held at one day plateaus when signs of physical withdrawal become apparent.

quantity, and pattern of drug use are noted. These are compared with the condition of the patient. He may be somnolent, normal, or else nervous and shaky depending on whether he has used more or less than his accustomed quantity of medication. In this manner an approximation can be made of the level of medication necessary to maintain this patient. Thus a safe transfer of the control of medications from patient to physician is assured and a comfortable withdrawal is possible.

The medications used by the patient during the period of the drug profile are divided into categories of narcotics, barbiturates, and others. Each category is totalled as equivalents of Methadone, phenobarbital, or other appropriate long-acting agents, to find the 24 hour requirement of long-acting medications. The long-acting medications are administered in four divided doses in a masking vehicle of constant volume on an exact time contingency basis, usually at 0600, 1200, 1800, and 2400 hours. This combination is called a pain cocktail. All analgesic and sedative medications are administered in this form. The content and strength of the pain cocktail is the only information kept secret from the patient. This is in order to eliminate all nonpharmacologic effects of the medications.

Considerable psychologic stress may occur on transfer from "prn" medication controlled by the patient to a secret pain cocktail over which the patient has lost control. Since the long-acting agents in the pain cocktail are slower in onset and last longer at the same effective daily dose, the patient will miss the "high" feeling associated with the rapid onset of a momentarily much higher blood level of a short-acting analgesic agent (Fig. 2*b*). He may feel that he is losing control of his ability to manipulate his environment. In order to avoid the panic exit from the program, a slight increase of about 20 per cent in levels of medication during this adjustment is recommended.

As soon as the patient is stabilized on the initial strength of pain cocktail, the concentration of its ingredients is reduced at the rate of 10 to 15 per cent of the initial dose per day in the case of narcotics and 5 to 10 per cent per day in the case of barbiturates (Fig. 2*c*). If physical signs of withdrawal occur the reduction is not made for that day. This mode of withdrawal is smooth and comfortable, yet rapid enough for a diagnostic program. During a long-term therapeutic program a longer time may be taken and the medication concentration even increased at times appropriate to exercise and other factors.[6]

It is the author's opinion that all patients with the CPS have a basic disturbance in their circadian rhythms. During the process of withdrawal an attempt is made to restore a normal day-night cycle by encouraging structured daytime activity. Patients are kept out of bed when possible during the day and Benadryl, which on this regimen produces sleep, is given at bedtime. Dr. Seres of the Portland Pain Rehabilitation Center even discourages daytime television watching. It is a measure of the significance of the analgesic abuse problem in maintaining the CPS that about two-thirds of patients on this withdrawal regimen stop complaining of pain shortly after medication control is established. The remaining one-third become more specific in their pain complaints and generally more diagnosable.

Diagnostic tests not requiring the patient's active participation, such as x-rays and bone scans, may be performed during the initial phase of the medication control (Fig. 2, *a* and *b*). Procedures requiring subjective responses, analysis of body chemistry, or measurement of muscle activity such as cystometrograms and strength testing are best left until 10 days to 2 weeks following the start of the decrease in medication, or until the patient appears symptomatically free of the effects of medication. These patients characteristically volunteer that they feel much better and that their thinking processes are much clearer in about a week to 10 days. This improvement will continue long after the withdrawal of analgesic intake is complete and the patient is taking only a blank cocktail. Patients with a long history of analgesic abuse will still report improvement in mental function and general well being many months later.

Unless the patient's environment outside the hospital can be altered, the likelihood of a return to the former life style of dependency and analgesic abuse is very great. An attempt is made to alter the patient's home environment by education of the immediate family in the learning factors associated with chronic pain behavior. The response of important people around the patient to the patient's pain complaints can determine the course of his illness.[6, 7] The severity of the pain and the related functional impairment may be increased without any change in the underlying pathologic state. To avoid this, the immediate family is counselled in recognition of the environmental reinforcers of the patient's pain behavior. The local physicians must be informed of the problem; all medications are removed from the home environment and the patient is discharged with a blank pain cocktail to take on a regular schedule. Doubtless the many advertisements promulgating drug use that we are exposed to every day encourage these individuals to return to a medication oriented life style. If medication is still indicated it

should be supplied through the medium of a secret pain cocktail available only from one source, usually the family physician.

TREATMENT OF CHRONIC PAIN

The treatment of chronic pain requires a clear understanding of the cause of the pain and application of a therapy intended to produce the maximum relief from suffering, while at the same time having the minimum complications. Especially in the case of the multifaceted Chronic Pain Syndrome, environmental as well as psychologic and behavioral factors have to be considered, in addition to the usual somatogenic, or physical causes of suffering. Each of these factors require a different therapeutic approach, often administered by different, unrelated groups of health care professionals. When multiple factors are present, a coordinated multidisciplinary team approach is best for efficient interference-free management encompassing two or more different health care specialities. In such a milieu, care must be taken so that the patient is not exposed to conflicting statements or implied differences of opinion from staff members, since this may have a profound effect on the patient's well being.

After an existing medication problem has been controlled, many previously difficult appearing pain problems will require only occasional psychologic supportive maintenance from the family physician. Some will be redefined as manageable within one health care speciality such as dentistry or orthopedics; others will remain truly intractable and remain as problems encompassing many disciplines. Some suggestions will be made for management of the environmental, psychologic, and somatogenic aspects of these patients.

Environmental stress either at home or at work can be a major factor in maintenance of the CPS. Injury related and disability dependent compensation must be included.[16] These problems can be very responsive to correct treatment, which should be started early in the management of these patients. Some patients will assume the role of a passive partner in the treatment process. This often blocks improvement and can confound the most vigorous therapy. With other patients, the simple explanation of an environmental stress can provide sufficient insight to permit them to solve their problems by themselves. Since this may not result in as satisfactory long-term improvement as when outside professional help is involved, it is still advisable to obtain a consultation. Environmental factors should not be modified casually, since a major alteration in life style, such as change of job, divorce, or giving up a pending lawsuit may be involved. Resources available for treatment in this area include family and marital counsellors, social workers, and clinical psychologists. Many industries employ counsellors familiar with their occupational problems. The professional qualifications and reputation of these individuals should be known before they are recommended to your patients.

Psychoses, neuroses, and personality disorders may play a significant role in the CPS. A pain complaint is likely to be associated with ei-

ther anxiety hysteria or reactive depression.[19] There is, however, a tendency for depressed patients to complain of pain, thus concealing their true problem of depression. The depression involved may be a primary disorder or secondary to environmental stresses or medication excesses. All narcotic analgesics and the frequently prescribed drug, diazepam, have the side effects of general depression, which can severely potentiate any tendency for a neurotic or psychotic depression. Withdrawal from these medications and restoration of normal circadian rhythms are usually sufficient to cause enough recovery from depression to eliminate pain complaints. Tricyclic antidepressants, e.g., amitriptyline 75 to 150 mg per day in divided doses, have been found effective in many patients with CPS, not all of whom have shown significant depression on the MMPI, the Zung scale, or by clinical impression. When incorporated into the pain cocktail at the time of withdrawal, tricyclics appear to hasten pain relief. Sternbach has had success in some patients with a transactional approach treating the depression instead of the pain.[20]

A psychotic state is sometimes compensated for by a patient's heavy use of pain-bought medications. This will make itself apparent during withdrawal by bizarre behavior, hallucinations, or even a suicide attempt. This decompensation, warned of by an increase in symptomatology with withdrawal, requires management in a psychiatric unit.

Management of the psychoses, neuroses, and personality disorders seen in the chronic pain syndrome requires access to a clinical psychologist with skill in using and interpreting the MMPI and other tests necessary to assess the patient. A psychiatrist interested in pain problems is an asset.

Behavioral factors and pain-related environmental manipulation often respond to the application of learning principles for the modification of pain behavior. The technique is that of contingency management or operant conditioning. When it is apparent that the somatogenic component or physical pain generator is minimal relative to the pain behavior, attention should be paid to exactly what the patient does or does not do and the resulting environmental consequences of his actions. By varying behavior reinforcers pain behaviors can be decreased and well behaviors increased. The family unit is programmed to sustain and reinforce this and the patient's social and work skills honed for his new life.[6-8] An established organization doing operant conditioning is the resource required for behavior modification, and this has been a successful therapy in selected patients.

Patients who continue to suffer because of a physical pain generator and who are not candidates for a definitive corrective procedure such as a discectomy or abscess drainage can obtain relief either through benign palliative procedures or nonspecific corrective measures. Since a definitive one-time cure rarely can be found, the philosophy of managing many of the patients on a continuing supportive basis must be adopted. Often sufficient treatment is to keep patients away from harmful surgery and medications.

A patient with inescapable physical pain can be taught to minimize his suffering if he can be shown what exacerbates his pain. The activity diary in which activity and severity of pain are noted hour by hour is a

useful tool for understanding the causal relationships of changing levels of pain. Reduction or avoidance can be planned of those activities which result in discomfort when indulged in with excess intensity or for too long a time. Administration of analgesics prior to predictably painful times of day so that their peak effect comes when most needed constitutes sensible use of medications.

Weight reduction is very important in the supportive management of skeletal-muscle problems. A contractual agreement can be made with the patient so that if he is not willing to help himself by losing weight and maintaining the new weight, you, as a physician, will not continue to help him. A weight check at the clinic door by the nurse will save a lot of useless discussion with the patient about weight losses.

Systemically administered analgesics are the most easily used palliative agents and are relatively inexpensive. They are, however, most prone to incorrect use by selection of the wrong drug or an improper dose. Nonnarcotic or antipyretic analgesics may be useful in control of mild pain. With more severe pain, codeine, alone or in combination with nonnarcotic analgesics, is useful. Excessively high prices may often be paid for heavily advertised combinations of inexpensive drugs that are no more effective than simple codeine and aspirin.

When analgesics are selected as the method of pain management, an optimum dose must be selected and varied as frequently as necessary. The optimum dose is the minimum quantity producing the desired effect while avoiding side effects. It can be determined only by observation of the effect, namely pain relief. This requires the skillful observation of all attending on the patient as well as the patient's report. The manufacturer's recommended dose is only a guide; it does not replace the decision making obligation of the physician. Halpern provides an excellent guide and reading list on this topic.[9]

Myofascial syndromes, characterized by the presence of so-called trigger areas in muscle or connective tissue, are a common somatogenic pain problem. Their management by interruption of the reflex pain cycle through dry needling (acupuncture), infiltration of local anesthetic, or spraying the skin with a vapocoolant is simple and can be readily managed in the usual office practice.[1]

Nerve blocks may be used in many areas of chronic pain from treatment of nerve entrapment syndromes to injections of inflamed bursae. Continuous epidural techniques can offer days of profound muscle relaxation as an aid to traction and bed rest for the herniated intervertebral disk. Sympathetic blocks, through unknown but possibly segmental spinal cord mechanisms, have been reported to provide months of symptomatic relief for chronic low back pain. Together with exercise, sympathetic blocks are definitive treatment for the causalgias and reflex sympathetic dystrophies. Nerve blocks, however, should be attempted only by an individual trained to handle their rare but potentially lethal complications.[2]

Mild stimulation of the skin is a common mode of chronic pain therapy that has stood the test of time, as evidenced by the counterirritant agents available in any drug store. More controllable electrical stimulation of the skin has proven effective in the management of many mild to

moderate chronic pain states.[12] It is so harmless and inexpensive that every victim of chronic pain should receive an adequate trial.

Patients with chronic, intractable pain problems may be recognized by the mnemonic SHAFT, for the *S*ad *H*ostile *A*nxious *F*rustrating patient who *T*enaciously clings to the health care system. These patients require different management than patients with acute self-limiting problems. A clear understanding of the mechanisms involved in their suffering is necessary. Appropriate therapy must be cautiously applied and long-term continuing maintenance is often necessary.

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